CRITICAL CARE
SELF-ASSESSMENT PROGRAM

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2016 • BOOK 1

INFECTION CRITICAL CARE

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MESSAGE FROM THE EDITORS

Welcome to the Critical Care Self-Assessment Program (CCSAP), a new recertification component for the Board Certified Critical Care Pharmacist. ACCP has a long tradition of offering the best products for continuing pharmacy education and pharmacotherapy specialist certification. CCSAP continues that tradition by providing the latest in evidence-based information for the critical care practitioner or clinician.

In designing this series, the primary goal was to provide updates that would improve clinical pharmacy practice and patient outcomes. The process began with a careful review of the content outline developed by the Board of Pharmacy Specialties for the Critical Care Pharmacy Specialty Certification Examination. The 2016–2018 CCSAP chapters will therefore cover the domains of clinical skills and therapeutic management; practice administration and development; and information management and education. Specific content for individual releases in this series was organized on the basis of the systems and patient-care problems that might be expected of the board certified critical care pharmacy specialist. Finally, calls went out to recruit faculty panel chairs, authors, and reviewers committed to this new specialty and to the board certification process.

The presentation of information, and its incorporation into practice, was also given careful consideration. Inside this CCSAP book, you will find user-friendly formatting as well as graphic elements such as patient-care scenarios demonstrating the application of concepts, treatment algorithms, descriptions of pivotal studies that may change practice, and summative practice points. All releases in this series are available electronically, enhancing the portability of this product. Prominent in each chapter are hyperlinks to reference sources, assessment tools, guidelines and resources, data compilers such as PubMed, and even informational videos. Our hope is that this depth of information, ease of access, and emphasis on clinical application will have an immediate and positive impact on the care of patients in the ICU and other critical care settings.

We very much appreciate the efforts of all the contributors who lent their energy and expertise to this new series.

Bradley A. Boucher and Curtis E. Haas, series editors

Infection Critical Care I

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Continuing Pharmacy Education Credit: The American College of Clinical Pharmacy is accredited by the Accreditation Council for Pharmacy Education (ACPE) as a provider of continuing pharmacy education (CPE).

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Fungal Infections in the ICU

By Christine M. Groth, Pharm.D., BCPS;
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Reviewed by Russell E. Lewis, Pharm.D., FCCP, BCPS; and Bo Cheng, Pharm.D., BCPS

LEARNING OBJECTIVES

1. Classify a critically ill patient's risk of invasive fungal infection.
2. Construct an algorithm for routine surveillance of invasive fungal infections in the ICU.
3. Distinguish key considerations for a reasonable prophylactic, preemptive, or empiric antifungal therapy regimen for a patient in the ICU.
4. Justify antifungal treatment algorithms designed for the ICU based on current evidence.
5. Evaluate the newer antifungal agents and their relative advantages and disadvantages in the ICU setting.

ABBREVIATIONS IN THIS CHAPTER

Anti-Mn	Anti-mannan antibody
AST	Antifungal susceptibility testing
ECIL	European Conference on Infections in Leukemia
ESCMID	European Society of Clinical Microbiology and Infectious Diseases
IA	Invasive aspergillosis
IC	Invasive candidiasis
IDSA	Infectious Disease Society of America
IFI	Invasive fungal infection
Mn	Mannan antigen
TDM	Therapeutic drug monitoring

INTRODUCTION

Invasive fungal infections (IFIs) are becoming more prevalent as the use of immunosuppressing therapies in the management of malignancy, transplantation, and rheumatology expands. As the population ages and the survival of patients with multiple comorbidities and advanced disease increases, the rates of fungal infection are expected to continue to rise. The presence of multiple risk factors and severe illness makes patients admitted to the ICU particularly vulnerable to these infections.

Over the past 20 years, advances in the management of IFI include new antifungal agents, improved diagnostic testing, and the availability of susceptibility testing. Despite these improvements, outcomes remain poor and resistance to the currently available antifungals is increasing. Mortality rates associated with invasive candidiasis (IC) have been reported to be about 40% to 60% in ICU patients and 80% to 90% in patients with septic shock. These infections also place a significant financial burden on the health care system because of longer hospital stays, use of expensive therapies, and increased consumption of health care resources. The estimated cost of a single episode of candidemia is $25,000–$55,000 and a single hospitalization for aspergillosis is $60,000 (Kett 2011). Clinical pharmacists can play an important role in helping to recognize patients at risk of fungal infection, in providing safe and effective use of antifungal agents, and in reducing costs associated with this disease.

EPIDEMIOLOGY

Candida Species

Candida spp. are common normal flora found on mucosal surfaces. In the presence of mucosal barrier breakdown or immunosuppression, these organisms become significant pathogens that can lead to increased morbidity and mortality. Candidiasis encompasses a host of infections involving mucosal surfaces and the urinary tract, as well as more disseminated disease (e.g., sepsis, meningitis, endocarditis, intra-abdominal infections). Candidiasis is the leading cause of IFI, with 50% of cases occurring in ICU patients. The exact prevalence of these infections is elusive because of variations in surveys used, the number of centers involved, and the type of patients; however, many studies cite a prevalence of about 7 cases per 1000 ICU patients.

BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:

- General knowledge on the pathophysiology of critically ill patients
- Pharmacology and recommended doses of commonly used antifungal agents
- Basic pharmacokinetic/pharmacodynamic principles of antimicrobials
- Drug-drug interactions common through the CYP enzyme system
- Common procedures used to diagnose infection in the ICU

ADDITIONAL READINGS

The following free resources are available for readers wishing additional background information on this topic.

- IDSA. Treatment of Aspergillosis [homepage on the Internet].
- IDSA. Management of Candidiasis [homepage on the Internet].
- ESCMID. Guideline for the Diagnosis and Management of Candida Diseases 2012 [homepage on the Internet].
- Maertens J, Marchetti O, Herbrecht R, et al. European guidelines for antifungal management in leukemia and hematopoietic stem cell transplant recipients. Bone Marrow Transplant 2011;46:709-18.
- Lewis RE. Current concepts in antifungal pharmacology. Mayo Clinic Proceed 2011;86:805-17.
- Kullberg BJ, Arendrup MC. Invasive candidiasis. N Engl J Med 2015;373:1445-56.

Candida spp. are reported to be the fourth leading cause of blood stream infections overall and the third leading cause of these infections in ICU patients. A recent survey of national acute care hospitals found *Candida* spp. to be the leading cause of hospital-associated bloodstream infections (Magill 2014). This fits with the 5-fold increase in *Candida* bloodstream infections over the past 10 years and the tripling of fungal sepsis cases in the past few decades. In addition, an epidemiologic shift is occurring in the species causing disease. Although *Candida albicans* remains the most common species isolated, it now accounts for only about 50% of the pathogens seen in both hospital wards and ICUs. Rates of non-*albicans* species are increasing in North America; *C. glabrata* is the second most common pathogen isolated, followed by *C. parapsilosis*, which is commonly seen in patients with chronic catheter placement (e.g., total parenteral nutrition). The rates of *C. tropicalis*, *C. krusei*, and *C. lusitaniae* remain stable, and these are still considered important pathogens. This shift in epidemiology has significant implications because non-*albicans* species often have either reduced susceptibility or resistance to fluconazole, a fungistatic drug commonly used preemptively to treat these infections.

Mold Pathogens

Invasive mold infections, particularly caused by *Aspergillus* spp., are also common among critically ill patients. Traditionally, invasive aspergillosis (IA) was thought to be a disease found mainly in neutropenic and hematopoietic stem cell transplant patients. However, the current understanding is that IA is also an important pathogen in non-neutropenic critically ill patients, such as those receiving corticosteroids and those with chronic lung diseases or liver failure.

Aspergillus spp. usually cause pulmonary or sinus disease, although infections of the skin and CNS may occur. Because infection usually starts from inhalation of the conidia, outbreaks of *Aspergillus* have been linked to poor air filtration, construction, and even contaminated medical equipment and hand lotion. The prevalence of IA in ICU patients has been reported to be 0.335% to 6.9%. This wide range is a result of the difficulties in diagnosing infection, as well as a lack of post-mortem reports confirming disease presence. Diagnosing IA in critically ill patients is particularly challenging because classic radiographic signs (e.g., halo sign or air crescent) are not always present in non-neutropenic patients, who do not progress as rapidly to angioinvasive disease. This challenge also explains why diagnostic studies tend to be less sensitive in non-neutropenic patients, further limiting methods for early detection of infection.

Similar to IC, IA is also associated with significant mortality and increased health-care costs. The average mortality rates in ICU patients with IA are 60% to 90%. This high mortality is not completely driven by severity of underlying illness, based on the finding that mortality rates appear similar

between those considered immunocompetent and hematopoietic stem cell transplant recipients with IA.

Other fungal pathogens causing disease in patients with immunocompromise include *Cryptococcus* spp., *Fusarium* spp., *Scedosporium* spp., and *Mucormycoses* spp. These infections are rare in ICU patients but occur more often in patients receiving chronic immunologic therapy for rheumatologic and other chronic conditions. Such infections present particular therapeutic challenges because they are associated with very high mortality.

High-Risk Patient Populations

It is now well recognized that IFIs are not limited to patients with severe immunosuppression. Critically ill patients have dysfunctional monocytes, macrophages, and impaired neutrophils that put them at risk of these opportunistic pathogens. Risk factors for IFI in the ICU are listed in Box 1-1. The prevalence of these risk factors in ICU patients complicates the decision of when to use prophylactic or preemptive antifungal therapy. Risk prediction models and clinical decision tools have been developed, but these have not been adequately evaluated in prospective multi-center trials. These algorithms have limited diagnostic applicability because of their low positive predictive values, impracticality, and tendency to promote overuse of antifungal agents.

Box 1-1. Risk Factors for Invasive Fungal Infections in the ICU

- Broad-spectrum antimicrobials
- Burns
- *Candida* colonization
- Central venous or urinary catheter
- Chemotherapy
- Corticosteroids
- Diabetes mellitus
- Graft-versus-host disease
- Hematopoietic stem cell transplant
- Hemodialysis
- High severity of illness (APACHE II >20)
- Immunosuppressing therapies
- Liver failure
- Major surgery
- Malignancy
- Mucosal damage
- Necrotizing pancreatitis
- Neonates
- Neutropenia
- Prolonged duration of ICU stay
- Prolonged ventilation
- Renal failure
- Solid organ transplant
- Structural lung disease
- Total parenteral nutrition

There is a strong correlation between *Candida* colonization and infection. Rates of colonization increase with longer ICU stays and exposure to risk factors. Most patients who develop IC are colonized to some degree, but only about 5% to 30% of colonized patients develop systemic infection. The *Candida* Colonization Index was developed in surgical ICU patients to evaluate the risk of developing IC in colonized patients. A ratio of the number of colonized sites to the number of cultured sites (e.g., urine, sputum, stool) greater than 0.5 is associated with an increased risk of IC. Using this threshold to start empiric antifungal therapy significantly reduced the incidence of infection compared with historical controls; however, most patients (87%) received preemptive treatment with fluconazole (Piarroux 2004). The concerns with using this index are its low positive predictive value (9%) and the increased use of antifungals, as well as the increased costs and workload associated with obtaining multiple cultures. It is also unknown how this model would apply to other ICU populations.

Other clinical prediction tools that incorporate several risk factors into a scoring system have been evaluated for their ability to predict IC (Table 1-1). These tools have good negative predicative values, making them useful in deterring antifungal therapy if risk factors are not present. The low positive predictive values of these scores may increase the risk of unnecessary antifungal use and lead to increased costs and potential resistance. Therefore, it is important to use these tools in the patient populations for which they were intended and also to take into consideration the specific patient population in the clinician's own institution. A well-designed risk score that identifies subgroups of patients (similar to those being treated at the clinician's ICU) with increased risk over the general population can help in the decision to use preemptive therapy.

ADVANCES IN DIAGNOSIS OF FUNGAL INFECTIONS

Limitations of Traditional Culture and Radiologic Methods

Traditional methods for diagnosing fungal infections include clinical signs and symptoms, radiography, cultures, and histopathology. These methods have many limitations and may lead to significant delays in initiating appropriate treatment. Fungal infections often have a delayed clinical course with very nonspecific signs and symptoms. Classic radiographic signs (halo sign or macronodules) are not always present, particularly among patients with immunosuppression, and may not aid in detecting changes early in the course of disease. These radiographic features are also not specific for a particular pathogen, resulting in broad treatment.

Blood cultures remain the gold standard for diagnosing candidemia but are only about 50% sensitive for detecting *Candida* spp. and rarely grow *Aspergillus* spp. or other mold

Table 1-1. Clinical Prediction Scores for Invasive Candidiasis

Score (year)	Patient Population	Model Risk Factors	Cutoff Value	Sensitivity/ Specificity (%)	PPV (%)	NPV (%)
Dupont Score (1994)	Surgical ICU peritonitis	Female, upper GI tract origin of peritonitis, perioperative cardiovascular failure, antimicrobial therapy at least 48 hours before peritonitis onset	Grade C= at least three risk factors	84/50	67	72
Candida Score (2006)	Medical/ surgical ICUs for ≥ 7 days	Severe sepsis (2 points), major surgery (1 point), total parenteral nutrition (1 point), multi-focal *candida* colonization (1 point)	Score ≥ 3	81/74	16	98
Ostrosky Rule (2007, 2011)	Medical/ Surgical ICUs for ≥ 4 days	Major criteria: systemic antibiotic use days 1–3, central venous catheter Minor criteria: surgery, immunosuppressants, corticosteroids, pancreatitis, dialysis, total parenteral nutrition Modified to add mechanical ventilation for at least 48 hours as an additional major criteria	Two major factors Two major + at least one minor factor One major + at least two minor factors Three major factors + at least one minor factor	89/38 66/69 34/90 50/83	4 6 10 10	99 98 97 97
Nebraska Medical Center Rule (2011)	Medical/ Surgical ICUs for ≥ 4 days	Broad spectrum antibiotics (1.5 points), central venous catheter (0.9 points), and total parenteral nutrition days 1–3 (0.9 points), steroid use in the 7 days before ICU admission up to day 3 (0.4 points), abdominal surgery (0.9 points), and pre-ICU length of stay x 0.039	Score ≥ 2.45	84.1/60.2	4.7	99.4
Candidemia Rule (2015)	All hospitalized patients with culture positive severe sepsis or septic shock	Antibiotics within 30 days, central venous catheter, admitted from nursing home, or total parenteral nutrition (2 points each), transferred from outside hospital or receiving mechanical ventilation (1 point each), lung as presumed source of sepsis (subtract 6 points)	Score ≥ 3	87.6/55.9	18.5	97.5

NPV = negative predicative value; PPV = positive predictive value.

Information from: Dupont H. Can yeast isolation in peritoneal fluid be predicted in intensive care unit patients with peritonitis? Crit Care Med 2003;31:752-57; León C. A bedside scoring system ("*Candida* score") for early antifungal treatment in non-neutropenic critically ill patients with *Candida* colonization. Crit Care Med 2006;34:730-7; Ostrosky-Zeichner L. Multicenter retrospective development and validation of a clinical prediction rule for nosocomial invasive candidiasis in the intensive care setting. Eur J Clin Microbiol Infect Dis 2007;26:271-6; Ostrosky-Zeichner L. Improvement of a clinical prediction rule for clinical trials on prophylaxis for invasive candidiasis in the intensive care unit. Mycoses 2011;54:46-51; Hermsen ED, Zapapas MK, Maiefski M, et al. Validation and comparison of clinical prediction rules for invasive candidiasis in intensive care unit patients: a matched case-control study. Crit Care 2011;15:R198; and Vasquez Guillamet C, Vazquez R, Micek ST, et al. Development and validation of a clinical prediction rule for candidemia in hospitalized patients with severe sepsis and septic shock. J Crit Care 2015;30:715–20.

pathogens. Blood cultures also fail to detect deep-tissue infections and can take several days to yield a positive result. Deep tissues and fluid collections are invasive and challenging to obtain, making a histopathologic diagnosis difficult, especially in patients who are unstable or thrombocytopenic. Unless cultures are taken from sterile sites, it also is difficult to differentiate true infection from colonization.

Rapid Diagnostics

Several advances in rapid diagnostic tests for IFI have been made in the past several years (Table 1-2). These tests may diagnose fungal infections early before signs of infections develop. They also have improved sensitivity and specificity over traditional methods and could potentially be used in conjunction with risk prediction models to help guide preemptive

Table 1-2. Rapid Diagnostic Tests for Invasive Fungal Infections

Test	Application	Sensitivity %	Specificity %	Limitations
β-D-glucan	*Candida* spp. and *Aspergillus*	57–97	56–93	False-positive: glucan -contaminated tubes/gauze, cellulose-containing dialysis membranes/filters, contaminated albumin/IVIG with fungal elements, gram-positive infections, gut inflammation, some antibiotics (amoxicillin-clavulanic acid) Controversy surrounding optimal cutoff value
Mannan antigen/ Anti-mannan antibody	*Candida* spp. only	Mannan: 58 Anti-mannan: 59 Combination: 83	Mannan: 93 Anti-mannan: 83 Combination: 86	Positive results occur later in disease course Sensitivity varies depending on species Best results when used together Cutoff value unclear
Nucleic-acid PCR	All species, but only available currently for *Candida* spp.	96	97	Using test too early may decrease sensitivity Unavailable for many organisms
Galactomannan	*Aspergillus* and some other molds	Serum: 71 BAL: 76–88	Serum: 89 BAL: 87–100	False-positive: β-lactams, Plasma-Lyte Not as sensitive in non-neutropenic patients

IVIG = intravenous immunoglobulin; PCR = polymerase chain reaction.

Information from: León C. What's new in the clinical and diagnostic management of invasive candidiasis in critically ill patients. Int Care Med 2014;40:808-19; and Perfect JR. Fungal diagnosis: how do we do it and can we do better? Curr Med Res Opin 2013;29:3-11.

therapy to target a specific organism, helping limit unnecessary antifungal use.

There are now several rapid diagnostic tests for the detection and identification of *Candida* spp. β-D-glucan is a cell wall constituent of *Candida* spp., as well as other fungi (but not *Cryptococcus* and *Zygomycetes*). The β-D-glucan diagnostic test is an assay that detects activation of the coagulation cascade by β-D-glucan. A meta-analysis reported a sensitivity and specificity of 57%–97% and 56%–93%, respectively, for the diagnosis of IC (Karageorgopoulos 2011). This assay has been shown to detect intra-abdominal candidiasis 5 days earlier than traditional methods. Also, it has a good negative predictive value (80% or greater), making it a potentially useful tool to prevent unnecessary use of antifungals.

False-positive results may occur because of glucan-contaminated collection tubes or gauze dressings, cellulose-containing dialysis membranes or products with cellulose filters, contaminated albumin or intravenous immunoglobulin with fungal elements, gram-positive infections (e.g., *Streptococcus pneumoniae*), gut inflammation, and antibiotics such as amoxicillin/clavulanic acid. Therefore, the positive predictive value of the test is often a limitation, reported in one study at 30% when a cutoff of two consecutive tests > 80 pg/mL was used (Hanson 2012). The recommended cutoff value is a single test result greater than 80 pg/mL or two consecutive tests > 60 pg/mL if serial monitoring is being used. Higher values (greater than 150 pg/mL for a single test or > 80 pg/mL for consecutive testing) have been suggested for critically ill patients. Two consecutive results (twice within a week) above this threshold are recommended to improve the diagnostic accuracy of this test.

Both the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and the European Conference on Infection in Leukaemia (ECIL) recommend the β-D-glucan diagnostic test as an adjunct to culture; however, it is important to keep in mind that most of the literature evaluating this test is in the setting of hematologic malignancy or surgical ICU patients. The ICU population has also been cited as a group more prone to false-positive results, further complicating interpretation. The accuracy of this assay in other ICU populations has yet to be determined, and the usefulness of serial monitoring of concentrations in guiding treatment response remains unclear, although some initial reports with echinocandin treatment appear promising.

Mannan is a polysaccharide component of the fungal cell wall that is specific to *Candida* spp. A commercially available latex agglutination and enzyme immunoassay exists for both mannan antigen (Mn) and anti-mannan antibodies (Anti-Mn)

that develop in response to mannan. Both tests are more specific than the β-D-glucan diagnostic test, but they are not as sensitive and do not become positive until later in the course of disease. A recent meta-analysis that included several studies in critically ill patients who were non-neutropenic found improved sensitivity and specificity of both tests when used in combination. It also demonstrated the sensitivity of the test varied based on *Candida* spp., with the highest sensitivity reported for *C. albicans* and the lowest for *C. parapsilosis* and *C. krusei* (Mikulska 2010). The reason for this finding is likely because of the different amounts of mannan produced and released by these organisms. It is also important to note that the studies included are limited by their retrospective design in a heterogeneous patient population, as well as by differences in definitions, diagnostic criteria, and cutoff values. The combined Mn and anti-Mn test is recommended by both the ESCMID and ECIL to detect candidemia and hepatosplenic candidiasis.

Galactomannan is an assay similar to Mn but is specific for *Aspergillus* spp. and a few other molds. Serial measurements are recommended in high-risk patients to guide preemptive therapy and potentially diagnose infection long before clinical symptoms develop. Serum samples have a reported sensitivity and specificity of 71% and 89%, respectively, in hematologic malignancy patients. The positive predictive value of this assay is less robust in solid organ transplant and non-neutropenic ICU patients, likely because of a lower prevalence of disease. The risk of obtaining a false-negative result depends on the optical density cutoff value used (optimal value is 0.5), as well as the presence or recent use of antifungal therapy, the degree of fungal burden, the presence of a walled-off infection, and the immunologic status of the patient. Non-neutropenic patients may be more likely to have a negative test result because of the slow progression to angioinvasive forms of the disease compared with the neutropenic population. False-positive results may occur while receiving β-lactams (piperacillin/tazobactam) or Plasma-Lyte. This test can now be performed directly from bronchoalveolar lavage samples, which tends to increase the sensitivity and specificity over serum values in non-neutropenic patients.

Another important tool for diagnosing IFI is the detection of fungal nucleic acids by polymerase chain reaction. Currently an FDA-approved assay is available for detecting *Candida* spp. only. This test allows for the early detection of candidemia and may be better than culture in detecting nonviable organisms and deep-seated infections. This assay has been reported to have a very high sensitivity (96.3%) and specificity (97.3%) in ICU patients, as well as good positive and negative predictive value (greater than 90%). Limited data are available regarding how colonization affects this test, but trends towards lower specificity have been seen. Also, using this test too early in the course of disease may lower its sensitivity. Despite these limitations, nucleic acid tests have the potential to be a very effective tool in the diagnosis of IFI.

A limitation of traditional blood cultures is the delay in time to positivity. After yeast grows, it takes several more days to identify the species and perform susceptibility testing. Use of molecular-based identification methods such as peptic nucleic acid fluorescence in situ hybridization (PNA FISH) can differentiate several of the most common *Candida* species with a turnaround time of only a few hours. Another technology, matrix-assisted laser desorption/ionization time of flight (MALDI-TOF) is capable of detecting some species of *Candida* directly from whole blood specimens, allowing even earlier initiation of treatment.

Although several advances have been made in rapid diagnostics for IFI, many unknowns remain, as do limitations in incorporating these tests for routine use, especially in ICU patients. These assays tend to be labor intensive, are not routinely available at many institutions, and have not been evaluated for cost-effectiveness. Other factors that must be considered include the degree of immunocompetence, type and site of fungal infection, timing of sample in relation to the clinical picture, and the presence of antifungal therapy or other factors that may interfere with the results. More data are needed regarding the optimal cutoff values for critically ill patients and whether one test or a combination of tests is best for guiding antifungal therapy.

Antifungal Susceptibility Testing

Antifungal susceptibility testing (AST) plays a vital role in determining resistance patterns and in guiding drug selection and de-escalation of antifungal therapy; however, knowledge about application of these testing results lags significantly behind those for bacteria. Standards for AST were recently updated to include the most commonly used drugs to treat IFIs.

Clinical breakpoints for *Candida* spp. and selected azoles are described as *susceptible*, *susceptible-dose dependent*, and *resistant* (Table 1-3). These breakpoints are based on pharmacokinetic-pharmacodynamic relationships and imply some correlation to clinical outcome. It is important to note that most of the clinical trial data supporting these breakpoints for fluconazole are flawed because of differences in the definition of treatment failure, the low number of non-*albicans* spp. and isolates with elevated MICs, and failure to account for differences in renal function for dose determination. Clinical data supporting breakpoints for voriconazole are from non-neutropenic patients.

A clear dose:MIC relationship that correlates with clinical outcome for azole therapy has not been established from the available literature. This lack of correlation makes it difficult to determine an appropriate treatment regimen for drugs with susceptible-dose dependent activity, which require higher-than-standard doses. Clinical breakpoints do not exist for *C. krusei* to fluconazole because of intrinsic resistance.

Table 1-3. Antifungal Susceptibility Breakpoints for *Candida* spp.

Antifungal Agent	Species	Susceptible (mcg/mL)	Susceptible-Dose Dependent (mcg/mL)	Resistant (mcg/mL)
Fluconazole	*C. albicans* *C. parapsilosis* *C. tropicalis*	≤ 2	4	≥ 8
	C. glabrata	n/a	≤ 32	≥ 64
	C. krusei	n/a	n/a	n/a
Posaconazole	All *candida* spp.	n/a	n/a	n/a
Voriconazole	*C. albicans* *C. parapsilosis* *C. tropicalis*	≤ 0.12	0.25–0.5	≥ 1
	C. glabrata	n/a	n/a	n/a
	C. krusei	≤ 0.5	1	≥ 2
Antifungal Agent	**Species**	**Susceptible (mcg/mL)**	**Intermediate (mcg/mL)**	**Resistant (mcg/mL)**
Anidulafungin	*C. albicans* *C. tropicalis* *C. krusei*	≤ 0.25	0.5	≥ 1
	C. parapsilosis *C. guilliermondii*	≤ 2	4	≥ 8
	C. glabrata	≤ 0.12	0.25	≥ 0.5
Caspofungin	*C. albicans* *C. tropicalis* *C. krusei*	≤ 0.25	0.5	≥ 1
	C. parapsilosis *C. guilliermondii*	≤ 2	4	≥ 8
	C. glabrata	≤ 0.12	0.25	≥ 0.5
Micafungin	*C. albicans* *C. tropicalis* *C. krusei*	≤ 0.25	0.5	≥ 1
	C. parapsilosis *C. guilliermondii*	≤ 2	4	≥ 8
	C. glabrata	≤ 0.06	0.12	≥ 0.25

n/a = not applicable.

Information from: Clinical and Laboratory Standards Institute M27–S4.

Susceptibility testing and clinical outcome have not been established for voriconazole to *C. glabrata* and posaconazole to any *Candida* spp.

Clinical breakpoints for *Candida* spp. and the echinocandins used to be reported as susceptible if 2 mcg/mL or lower and non-susceptible if above this threshold. The new breakpoints are now described as *susceptible*, *intermediate*, and *resistant* (see Table 1-3). These breakpoints were derived primarily from clinical trials in non-neutropenic patients. Overall, the echinocandin breakpoints are identical across the class. The exception is micafungin and *C. glabrata*, for which lower breakpoints are used based on methodologic differences, and not differences in clinical efficacy between agents.

Much controversy surrounds the revision of these breakpoints and a lack of data correlating MIC with clinical outcome. The reason for this change in breakpoints is based on evidence suggesting that the presence of resistance mutations may better correlate with response to therapy than the actual MIC. Many reports identify hotspot genetic mutations leading to echinocandin resistance in some *Candida* spp. that have

lower MICs than the previously reported susceptibility cutoff of 2 mcg/mL. Therefore, the previous cutoff value failed to identify which isolates carry these resistant mutations, and the new clinical breakpoints have been lowered to help segregate wild-type isolates from ones with mutations. Several institutions have also reported increased caspofungin MICs (specifically in *C. glabrata*) above the new cutoffs that would be considered resistant, but these cases responded to echinocandin therapy. This finding demonstrates that elevated MICs do not necessarily imply poor outcome and further reduces the reliability of the breakpoints to help guide therapy. Recent literature suggests micafungin or anidulafungin may be more reliable than caspofungin to detect resistant mutations and predict treatment failure even in those treated with caspofungin (Shields 2013).

Resistance

Resistance to the commonly used antifungal agents among both yeast and mold species is an area of ongoing investigation. With the introduction and increased use of AST, the detection of resistance amongst identifiable species is now possible. Overall, resistance rates for most species are low but are trending upwards. Even more concerning are the increasing rates of drug resistance in treatment-naïve patients. This shift is in part a result of selective pressure from increased use of antifungals in the prophylaxis of patients with immunocompromise; increased preemptive and empiric use, particularly in ICU patients because of poor diagnostics; overuse of antifungals in the community for treating minor fungal infections; and widespread use of agricultural fungicides.

Fluconazole resistance in *C. albicans* is very rare (less than 5% of isolates). Resistance to other species of *Candida* is increasing, with rates approaching 10% for several common species. Intrinsic resistance of some *Candida* spp. (e.g., *C. krusei*) to fluconazole is well known. For other species/medication pairs, it is less clear. For example, *C. parapsilosis* has been reported to have higher MICs to the echinocandins than other *Candida* spp., but this finding has not resulted in treatment failure in clinical trials. About 20% to 30% of candidemia cases involve intrinsically resistant species, and prior use of antifungals is the most common risk factor for selecting these pathogens.

Acquired resistance, or resistance that develops during therapy, is more difficult to predict, and much remains to be elucidated. Acquired resistance has been reported during treatment of *Candida* infections, particularly *C. glabrata*, with fluconazole. These species are often cross-resistant to other azoles and may even display multi-drug resistant phenotypes. Acquired resistance to echinocandins has also been noted in patients receiving long-term therapy for *Candida* infections. *Candida* resistance to amphotericin B is rare (1%–3% of isolates) but difficult to determine because of inadequate susceptibility testing methods. In Europe, *C. glabrata* and *C. krusei* typically have higher MICs to amphotericin B, and increasing rates of resistance to polyenes are being reported.

Less is known about resistance patterns in *Aspergillus* spp., likely because of a lack of national surveillance programs, routine susceptibility testing, and species identification. The reported prevalence of resistance to the mold-active azoles varies geographically but has been reported on average to be about 4% for *A. fumigatus*. Higher rates of resistance are found in some European and Asian countries, likely a result of increased agricultural use of azole fungicides in these areas. Some of the more rare species of *Aspergillus* (e.g., *A. terreus*, *A. flavus*) are intrinsically resistant to amphotericin B. Variable resistance to the echinocandins has been reported with these species. Resistance may develop to azoles during long-term therapy for the treatment of chronic or allergic forms of aspergillosis. Acquired resistance to amphotericin B and the echinocandins is rare, but this may be underreported because of a lack of susceptibility testing.

Resistance mechanisms found in fungal pathogens include the induction of efflux pumps and genetic mutations or increased expression of genes encoding these mechanisms. Biofilms are also an important cause of resistance in *Candida* spp. because of poor penetration of azoles into these complex cellular matrixes. *Aspergillus* spp. also form biofilms in the lung that contribute to the difficulty in treating these infections. The common mechanisms for each class of antifungal drug are listed in Table 1-4.

Much more evidence is required for a full understanding of antifungal resistance. The rates of infection from resistant species are increasing, and there are limited options available to treat these pathogens. To combat this growing problem will require improvements in AST that better correlate MIC values with clinical efficacy, as well as the discovery of molecular methods for detecting resistant mutations.

EVIDENCE-BASED APPROACH TO INVASIVE CANDIDIASIS TREATMENT

Delays in initiating appropriate antifungal therapy negatively affect survival in critically ill patients with IFI. Several challenges exist in confirming a definitive diagnosis of these infections and in identifying high-risk patients. Therefore, a strategy to prevent these infections or preemptively treat them is warranted.

Prophylactic Therapy

The 2009 Infectious Disease Society of America (IDSA) guidelines for the management of IC support a prophylactic approach to prevent disease in high-risk patients. In several single center studies and meta-analyses, the use of prophylactic fluconazole therapy in ICU patients reduced the incidence of *Candida* infections by about 50%; however, this strategy had questionable mortality benefit because of conflicting results and the heterogeneity of the populations studied.

Table 1-4. Common Antifungal Resistance Mechanisms

Drug Class	Site of Action	Resistance Mechanism	Implications
Azoles	Inhibit lanosterol-14α-demethylase ERG11 Candida CYP51 Aspergillus	Up-regulation of efflux pumps ABC transporters/CDR1,CDR2 genes TAC1 transcription factors Up-regulation of efflux pumps MFS transporters/MDR1 gene MRR1 transcription factors ERG11 and CYP51 mutations ERG11 and CYP51 overexpression ERG3 inactivation Biofilm formation Increase in cell wall chitin content	Decrease drug entry into cell (all azoles) Decrease drug entry into cell (fluconazole) Decrease binding affinity, increase MIC Counteract drug effects Ergosterol replaced by another sterol (cross-resistance all azoles) Inhibit drug penetration Increase tolerance to drug
Echinocandins	Inhibit Fksp catalytic subunit of (1,3)-β-D-glucan synthase	FKS1 and FKS2 mutations Increase in cell wall chitin content	Alter catalytic capacity, increase MIC (cross-resistance to entire class) Increase tolerance to drug, paradoxical growth May correlate better with response to therapy than actual MIC
Polyenes	Bind ergosterol Induce oxidative stress	ERG2, ERG3, ERG5, ERG6, ERG11mutations Increase in anti-oxidative enzymes Alteration in production of free radicals	Decrease ergosterol biosynthesis Decrease oxidative stress

ABC = ATP-binding cassette; MFS = major facilitator superfamily.

Information from Spampinato C. *Candida* infections, causes, targets, and resistance mechanisms: Traditional and alternative antifungal agents. Biomed Res Int 2013:204237; Cuenca-Estrella, M. Antifungal drug resistance mechanisms in pathogenic fungi: from bench to bedside. Clin Microbiol Infect 2014;20(suppl 6):54-9; and Maubon D. Resistance of *Candida* spp. to antifungal drugs in the ICU: where are we now? Int Care Med 2014;40:1241-55.

This approach would require administering antifungal therapy to hundreds of patients to prevent one infection. Administering prophylactic fluconazole therapy to a broad population of ICU patients has the potential to increase resistance and select fluconazole-resistant species, which may result in breakthrough infections. Prophylactic therapy might also mask poor infection control procedures, especially with central venous catheters and prolonged use of Foley catheters. This risk outside of the ICU has been clearly documented in patients with HIV (for esophageal candidiasis) and cancer, as well as in transplant recipients. Data supporting this concern in ICU patients have been inconclusive.

A recent retrospective study was performed in a surgical ICU in France, where 13% of the population received preemptive fluconazole therapy for high-grade *Candida* colonization. An evaluation of colonization trends over an 8-year period found a significant increase in acquired *C. glabrata* colonization and a decrease in *C. parapsilosis* colonization clearing; however, changes in susceptibility were not evaluated (Ferreira 2015). Current recommendations in the IDSA guidelines are to administer prophylactic fluconazole therapy only to those patients with a 10% or higher risk of infection as determined by a risk prediction score.

Identifying high-risk patients who may benefit from prophylactic therapy remains a challenge. As previously mentioned, risk prediction scores tend to overestimate the number of patients who would benefit from this strategy. One particular at-risk group includes those recently undergoing intra-abdominal surgery with recurrent anastomotic leakages. Prophylactic antifungal therapy has been shown to reduce the incidence of intra-abdominal candidiasis in these patients.

A multi-center, randomized, double-blind, placebo-controlled study evaluated the use of caspofungin to prevent IC; a previously validated risk prediction tool (Ostrosky Rule Modified 2011) was used to identify patients at high risk of infection. There was a reduction in the rate of proven or probable infection with prophylactic caspofungin (n=102) versus placebo (n=84), (9.8% and 16.7% respectively, p=0.14), but this did not reach statistical significance (Ostrosky-Zeichner 2014). However, the study was likely underpowered based on the lower-than-expected rate of invasive disease found in the placebo arm.

Finally, only a few studies have evaluated the use of an echinocandin for prophylaxis; most of the data are with fluconazole. Until more data are available, the choice of drug for prophylactic therapy should depend on the epidemiology of *Candida* spp. at the institutional level.

Empiric Therapy

An empiric therapy approach involves waiting until a patient displays signs and symptoms of infection before starting antimicrobials. This strategy avoids the widespread use of prophylactic therapy but may provide therapy too late in the course of disease. Furthermore, once empiric therapy is started it is difficult to determine when to stop therapy if a definitive diagnosis is not made on the basis of culture results. Delaying appropriate antifungal therapy has been associated with worse outcomes, but data indicating improved survival with early empiric therapy are lacking. Guidelines for empiric therapy for IC are available from the IDSA and are similar to the treatment recommendations discussed in the following section.

Preemptive Therapy

Preemptive therapy may be a more promising approach to managing IFI, especially in ICU patients. This strategy involves using diagnostic markers to screen high-risk patients before or just as symptoms begin to develop. This screening limits the number of patients exposed to drug therapy but also catches patients earlier in the course of disease. As with prophylactic therapy, the problem lies in which patients to target. An unpublished study (INTENSE NCT01122368) comparing micafungin versus placebo for preemptive treatment in high-risk surgical patients with intra-abdominal infections failed to show a difference in the incidence of IFI, mortality, or any improvement of organ function. This study was likely underpowered because of a low incidence of infection in the placebo arm during the treatment period. Also, the abdominal penetration of echinocandins has recently been called into question.

A team looking at the rate of resistant *Candida* spp. in patients with abdominal candidiasis with recent echinocandin exposure found the abdomen to be a reservoir for the growth of resistant *Candida* spp. (Shields 2014). This study found FKS mutant *Candida* spp. in 24% of patients with an overall echinocandin failure rate of 52%, which may explain the lack of benefit with micafungin in the INTENSE study.

Given that new rapid diagnostic tests are more readily available, a preemptive approach to managing IC using fungal specific antigens and nucleic acids may be more effective. One study demonstrated the feasibility of using (1,3)-β-D-glucan concentrations to guide preemptive therapy with anidulafungin (Hanson 2012). The prophylactic study mentioned earlier also evaluated the role of caspofungin in preventing IC using a preemptive approach (Ostrosky-Zeichner 2014). Subjects were screened twice weekly with (1,3)-β-D-glucan concentrations. Two consecutive concentrations of 80 pg/mL or greater were considered diagnostic for IC. Using this approach, the rate of proven or probable IC was significantly reduced in subjects receiving caspofungin versus placebo (18.8% vs. 30.4% respectively, p=0.04). However, no significant differences in mortality or length of stay were observed. This calls into question the utility of using this biomarker, at a cutoff of 80 pg/mL, as a diagnostic tool; it also leads to consideration of whether a higher cutoff should be used for ICU patients.

The FUNGINOS study prospectively assessed the utility of the β-D-glucan diagnostic test versus other diagnostic tests in diagnosing intra-abdominal candidiasis in high-risk surgical patients. In patients with GI perforation, two consecutive β-D-glucan diagnostic tests greater than 80 pg/mL were superior to the *Candida* Score and Colonization Indexes in discriminating candidiasis from colonization with a 72% positive predictive value and 80% negative predictive value. Elevated β-D-glucan levels proceeded positive cultures and antibiotic therapy by a median of 5 and 6 days, respectively. Levels above 400 pg/mL predicted both severity of infection and worse outcome, and decreasing levels were seen in those responding to therapy (Tissot 2013). This study demonstrates the usefulness of the β-D-glucan diagnostic test in guiding preemptive therapy in a disease that is commonly culture negative.

Many challenges exist in identifying appropriate patients who would benefit from antifungal therapy in the absence of definitive cultures. One approach to preemptive and empiric therapy using non-culture based diagnostic tests can be found in Figure 1-1. Further information is needed on the role of using (1,3)-β-D-glucan or other rapid diagnostics in initiating preemptive antifungal therapy in ICU patients, particularly to determine which patients to target and what cutoff values should be used in ICU patients to confirm diagnosis.

The EMPIRICUS trial (NCT01773876) aims to evaluate the efficacy of micafungin in improving IC-free survival in high-risk ICU patients with septic shock, multi-organ failure, and *Candida* colonization. This trial will also be looking at trends in serum biomarkers. The study is completed and once published, results and post hoc analysis of this study should help further delineate the role of both empiric and preemptive therapy.

TREATMENT STRATEGIES FOR PATIENTS WITH INVASIVE FUNGAL DISEASE

Candida Infections

Candidemia

The 2009 IDSA treatment guidelines for the management of IC (to be revised in the near future) recommend initial treatment with an echinocandin for moderately to severely

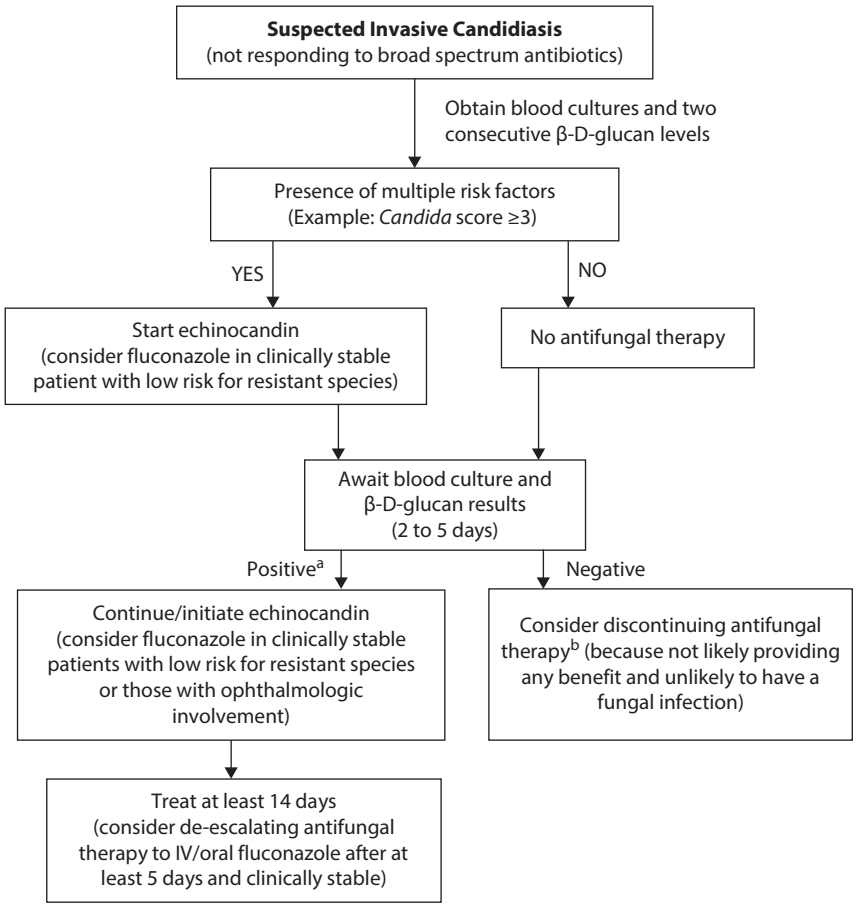

Figure 1-1. General approach to preemptive/empiric antifungal therapy.

[a]Positive β-D-glucan diagnostic test result is two consecutive tests > 80 pg/mL.

[b]If clinically improving on antifungal therapy, then consider a short course of therapy for no more than 7 days.

Information from: Blot S, Charles PE. Fungal sepsis in the ICU: are we doing better? Trends in incidence, diagnosis, and outcome. Minerva Anestesiol 2013;79:1396-405.

ill patients with candidemia and patients already receiving azole prophylaxis. The 2012 European guidelines strongly recommend an echinocandin as first-line treatment for all patients.

All the echinocandins have proven efficacy for the treatment of candidemia and are considered interchangeable for the management of this disease. One exception is in neutropenic patients, for whom caspofungin may be preferred for empiric therapy because of a lack of data with the other agents. Support for this class as first-line agents comes from the shift in epidemiology towards non-*albicans* spp. and low levels of resistance seen. Anidulafungin is superior to fluconazole for the treatment of candidemia caused by *C. albicans* and in patients with a high severity of illness. A meta-analysis of randomized trials evaluating antifungal therapy for the management of IC/candidemia indicated a survival benefit in subjects receiving echinocandin therapy versus those on polyenes or azoles (Andes 2009).

Fluconazole therapy can be considered for patients with mild disease in institutions with a low incidence of non-*albicans* spp. and fluconazole resistance. Voriconazole is also effective for candidemia, but adverse effects, drug-interactions, cost, and the potential for cross-resistance to fluconazole limit its use. Another role for fluconazole therapy is in the setting of ocular involvement of infection. Echinocandins have poor eye penetration; therefore an azole, if susceptible, would be preferred.

Treatment of candidemia should continue for at least 14 days after the first negative blood culture, but longer courses may be needed in the presence of abscesses or deep-tissue infections. The question of when to de-escalate to oral fluconazole therapy, if susceptible, is much debated.

The IDSA guidelines recommend at least 5 days of echinocandin therapy, but the European guidelines recommend 10 days based on recent data indicating a potential superiority over fluconazole. An open-label, non-comparative trial looked at the efficacy and safety of step-down therapy to an oral azole after 5 days of anidulafungin in patients who were afebrile, were hemodynamically stable, were non-neutropenic, had documented clearance of *Candida* from the bloodstream, and were able to tolerate oral therapy. This strategy resulted in a global response rate of 83.7% and was well tolerated (Vazquez 2014). Therefore, step-down to oral therapy is reasonable, taking into consideration the clinical condition and stability of the patient as well as source control when determining time course for de-escalation.

Determining and addressing the source of candidemia can be challenging in critically ill patients. The IDSA guidelines recommend that all patients with candidemia receive a dilated funduscopic examination within the first week of diagnosis to rule out optic involvement. Intravenous catheters are often the source; therefore, catheter removal should be considered. Symptoms should resolve within 72 hours, so the persistence of symptoms beyond this point should give reason to consider inadequate source control versus suboptimal drug exposure or resistance.

Intra-Abdominal Infections

As previously mentioned, patients undergoing intra-abdominal surgery are at increased risk of IC. About 30%–40% of patients with secondary or tertiary peritonitis will have *Candida* peritonitis or abscesses. There is a paucity of data related to the management of these infections, and standardized definitions and diagnostic criteria do not exist.

A recent multinational expert panel developed practice recommendations for the management of intra-abdominal candidiasis in immunocompetent patients (Bassetti 2013). Patients with suspected infections should have a culture taken during surgery or shortly after (less than 24 hours) a percutaneous drain is placed. Empiric therapy can be considered in patients with intra-abdominal infections and the presence of either risk factors or positive serologic markers for *Candida*. Definitive antifungal therapy is only recommended if *Candida* is recovered from an adequate specimen. Positive *Candida* cultures taken from drains placed more than 24 hours ago should be considered contamination and not be treated. Therapy with an echinocandin or lipid-based amphotericin B is preferred. Azole therapy, similar to treatment of candidemia, can be considered for mild disease or step-down therapy. Treatment should continue for 10–14 days in those with confirmed infection. Empiric therapy should be discontinued if *Candida* is not found after 3–5 days and the patient improves; or immediately if no improvement is seen, because the likelihood of any benefit is minimal. As mentioned previously, β-D-glucan levels may be useful in guiding treatment in this typically culture-negative disease by both helping to decipher true infection from colonization and assessing response to therapy.

Urinary Tract Infections

Isolation of *Candida* from the urinary tract of critically ill patients is common. The decision to treat is complicated by the inability to determine if classic signs and symptoms of infection are present. Most patients can simply be managed by removing the Foley catheter. Treatment with antifungal therapy should be considered in patients with sepsis of unknown origin; those with neutropenia; or those undergoing urologic procedures, because of the high risk for systemic disease.

Choice of antifungal agent is limited by poor penetration of most antifungals into the urine. Fluconazole remains the drug of choice, and treatment should continue for 14 days. Amphotericin B bladder washes are difficult to administer, and data supporting their efficacy are lacking. In one report, the procedure was associated with only transient clearance and higher overall mortality (Jacobs 1996).

Lung Infections

Although isolation of *Candida* spp. from the respiratory tract of critically ill patients is common, the occurrence of true pneumonia from this organism is rare because of innate mechanisms of defense within the lung. Diagnosis is challenging because of a lack of specific signs, symptoms, and radiographic findings; and because this requires lung biopsy. The decision to treat should be based on evidence of disseminated disease or host factors suggesting a high risk of infection with no other source. Specific host factors include neutropenia, hematopoietic stem cell transplant, immunosuppressing therapies, corticosteroids, and severe immunodeficiency. All of the available antifungal agents penetrate the lung well and are reasonable options. Empiric therapy with voriconazole may be preferred because aspergillosis is also a potential cause of lung infections in these patient populations.

Invasive Mold Infections

Prophylaxis and Empiric Treatment

Recommendations for the management of invasive mold infections in critically ill patients are largely extrapolated from data evaluating treatment in hematologic malignancies. Amphotericin B and its lipid formulations remain the most broad-spectrum antifungals available and should be strongly considered for empiric therapy in the setting of an unidentified mold infection or in patients on previous azole therapy. Voriconazole is now recommended as first-line therapy for *Aspergillus* infections. This recommendation is based on data indicating more successful outcomes and improved survival compared with amphotericin B, while causing less adverse effects.

The echinocandins have been shown to have activity against *Aspergillus*. Only caspofungin is approved for this indication, but all three agents have been used clinically.

Echinocandins are usually reserved for patients intolerant of other therapies or in refractory disease. However, more recent data regarding the combination of voriconazole and anidulafungin for treatment of IA suggest an earlier role for combination therapy including the echinocandins in patients with presumed IA.

Prophylactic therapy in non-neutropenic, immunocompetent patients cannot be recommended based on insufficient data. Empiric therapy should begin, even in those without traditional risk factors, at the earliest signs or clinical suspicion for IA. This approach is appropriate because delays in appropriate therapy for IA have been shown to increase length of stay, health care costs, and mortality. The use of biomarkers, mentioned earlier, may help identify patients that may benefit from antifungal therapy earlier. The optimal duration of treatment has not been determined. Most patients will require a prolonged course of several weeks based on resolution of clinical symptoms and radiographic findings.

Combination Therapy

Combination antifungal therapy for IA is recommended as an option for salvage therapy in patients not responding or with breakthrough symptoms. Up to 30% of ICU patients have been reported to have refractory disease, and observational studies have indicated up to 50% of patients often receive combination therapy. Typical combination regimens involve using two agents with different mechanisms of action, such as an echinocandin (cell wall target) with either an azole or amphotericin (cell membrane target). Because of the potential for antagonism, combination therapy with an azole and amphotericin is not recommended.

Despite the frequent use of combination therapy in the ICU for refractory IA, very few data exist supporting its benefit. Most data are derived from retrospective cohorts with very small sample sizes that reported conflicting outcomes. A prospective, randomized trial comparing the combination of voriconazole and anidulafungin with voriconazole alone demonstrated a trend towards reduced mortality in hematologic malignancy/hematopoietic stem cell transplant patients with combination therapy (Marr 2015). A post hoc subgroup analysis from this study indicated the greatest difference in mortality seen with combination therapy was in patients with baseline galactomannan optical density values of 0.5 to 1.5 and those treated with combination early in the course of disease.

ANTIFUNGAL PHARMACOTHERAPY

Amphotericin B

Amphotericin B, despite its toxicities, still remains an important treatment option for fungal infections in the critically ill. This agent has broad fungicidal activity against most fungal pathogens infecting patients in the ICU and is particularly useful for severe infections in patients with immunocompromise, with CNS infections, or when alternative options are limited by resistance, toxicities, or drug interactions.

Amphotericin B deoxycholate was the gold standard formulation until the 1990s, when three liposomal-based products (i.e., amphotericin B lipid complex, liposomal amphotericin B, and amphotericin B colloidal dispersion) were marketed. These newer formulations have similar efficacy but significantly less nephrotoxicity than the parent compound. The liposomal product is reported to have less nephrotoxicity than the other two lipid formulations; however, this finding does not appear to be clinically significant. Nephrotoxicity can be reduced with all amphotericin B products by adequately hydrating and sodium loading with a normal saline bolus (250–500 mL) before each dose and by avoiding concomitant nephrotoxic drugs, particularly diuretics. Continuous infusions of amphotericin B may prevent nephrotoxicity but should be avoided because the concentration-dependent pharmacodynamics of amphotericin B would not be optimized.

Lipid amphotericin products, with the exception of amphotericin B colloidal dispersion, have an approximate 50% lower rate of infusion-related reactions than the deoxycholate product. Because of the high rate of infusion reactions, the use of the colloidal dispersion product has fallen out of favor. Infusion-related reactions can be minimized with the use of acetaminophen and diphenhydramine 30 minutes before the infusion and should be considered standard of care. Another rare reaction reported with the liposomal product manifests with hypoxia, chest pain, flushing, and possibly flank pain and urticaria. These symptoms often mimic respiratory failure or an acute myocardial infarction. Clinicians should be aware of this reaction to minimize unnecessary escalation of care.

Electrolyte disorders commonly occur in critically ill patients. Amphotericin B therapy is nearly always associated with hypokalemia and hypomagnesemia. Just as amphotericin B binds to the fungal cell wall of ergosterol, thereby altering permeability, drug-tissue binding also can occur in mammalian renal cells and cause loss of potassium. Furthermore, hypomagnesemia can worsen potassium homeostasis. Close monitoring and repletion as necessary are recommended.

Echinocandins

In 2001, the first of the three available echinocandins was approved by the FDA and changed the way disseminated fungal infections are managed. These agents have a unique mechanism of action specific to the fungal cell wall. They provide fungicidal activity against *Candida* species and fungistatic activity against mold, as well as activity against biofilms. They are all equally efficacious and have minimal toxicity and drug interactions; therefore, choice of agent depends on institutional preference, cost, and the approved indications.

Adverse effects associated with the echinocandins are relatively benign, with rare reports of liver toxicity and infusion

reactions being of most concern. The infusion reaction reported with this class of antifungals is histamine-mediated and can be compared with the red man syndrome seen with vancomycin. Slowing down the infusion rate will prevent the reaction from recurring, and it typically subsides once the infusion is completed.

The echinocandins do not have any significant activity on CYP hepatic enzymes; therefore, drug interactions are minimal. Caspofungin and micafungin are reported to increase cyclosporine and tacrolimus serum concentrations. Because this drug interaction is minor, empiric dose reductions are not necessary; monitoring of serum concentrations is recommended.

Extended-Spectrum Triazoles

Voriconazole and posaconazole offer enhanced activity against *Candida* and other yeast, as well as a variety of mold pathogens. The addition of these agents expanded the treatment options for management of invasive fungal disease, including providing an oral treatment option. Despite their proven efficacy, several factors make the use of these drugs in the ICU a challenge.

Oral absorption of these agents can be significantly reduced depending on how they are administered. Voriconazole requires administration on an empty stomach because food can decrease absorption by 20%. It is recommended to hold tube feedings 1 hour before and 1 hour after administration. Posaconazole suspension, in contrast, should be given with a high-fat meal. In situations in which this approach is not possible, administering a high-fat nutritional supplement or administering posaconazole as 200 mg every 6 hours can provide similar plasma concentrations as giving 400 mg every 12 hours with a high-fat meal.

Gastric acid improves absorption of posaconazole; this can be optimized by administering it with ginger ale. Gastric acid suppression therapy is a concern in patients also receiving posaconazole suspension. Proton pump inhibitors should be avoided. H_2-antagonists may also reduce exposure but likely to a lesser degree. Most bioavailability data with H_2-antagonists indicating reduced absorption are with cimetidine; therefore, cimetidine should not be used concomitantly with posaconazole. Alternative agents such as famotidine and ranitidine have conflicting data, but these agents are preferred over a proton pump inhibitor. Posaconazole delayed-release tablets improve absorption, but this approach is not an option for most ICU patients because the tablets cannot be given in a nasogastric tube. Patients already taking these tablets must be switched to the suspension; however, plasma concentrations of the suspension will be reduced when given through a nasogastric tube. Recommendations for dose adjustments do not exist; therefore, close monitoring of clinical effect or therapeutic drug monitoring (TDM) may be necessary. An intravenous formulation of posaconazole was recently approved that will likely be a better option for ICU patients requiring this antifungal. It requires only a once-daily dose after the initial loading dose, but it will require a central line and has a short stability.

Voriconazole and posaconazole, like all azoles, can cause hepatotoxicity, adrenal suppression, and QT prolongation. In addition, voriconazole has been known to cause significant visual disturbances as well as a theoretical risk of renal toxicity with the intravenous formulation. Visual disturbances occur with oral and intravenous therapy and are usually transient, with patients adjusting to them after 1–2 weeks of therapy. These vision issues are typically related to the initiation and temporal administration of the drug and have been described as bright flashing lights or hallucinations.

The intravenous formulation of voriconazole contains a second-generation cyclodextrin-solubilizing agent. First-generation cyclodextrins have been shown to cause renal toxicity and can accumulate in renal failure. It is therefore recommended to use oral voriconazole when possible in patients with CrCl less than 50 mL/min. Multiple studies addressing the risk of nephrotoxicity with intravenous voriconazole have failed to show a correlation, and recent safety data with second-generation cyclodextrins show poor penetration into renal tubular cells and no risk of toxicity. In addition, hemodialysis appears to remove cyclodextrin to a considerable extent. Based on this information and experience from pre-marketing trials, it is reasonable to use intravenous voriconazole in patients with reduced renal function when the benefit exceeds this theoretical risk.

All azole antifungals inhibit CYP hepatic enzymes, with voriconazole and posaconazole being strong inhibitors of CYP3A4. This inhibition may lead to significant increases in cyclosporine, tacrolimus, and sirolimus serum concentrations. The interaction with sirolimus is of particular concern because the increases in drug exposure are completely unpredictable. Concurrent administration of sirolimus with these newer azoles requires frequent concentration monitoring if the combination cannot be avoided. Additional clinically relevant drug interactions that may occur in critically ill patients receiving voriconazole or posaconazole include increased exposure to fentanyl, midazolam, phenytoin, corticosteroids, quetiapine, and warfarin.

Voriconazole is a substrate and moderate inhibitor of CYP2C19. Voriconazole should be used with caution in combination with strong inhibitors or inducers of CYP2C19, such as rifampin, and with drugs metabolized by CYP2C19, such as clopidogrel. This route of metabolism combined with non-linear pharmacokinetics can make voriconazole dose adjustments challenging in the setting of a complicated critical care regimen.

Lastly, because of the risks of QT prolongation, administration of azoles with other moderate to strong QT-prolonging drugs should be monitored closely or avoided.

Dose Considerations

Inadequate doses of antimicrobials are common in the ICU because of the pharmacokinetic-pharmacodynamic changes that occur in critically ill patients (e.g., increased volume of distribution, enhanced elimination). This inadequacy may lead to treatment failure, increased resistance, and worsened outcomes. Fluconazole is often under-dosed when loading doses are not given and when fixed (400-mg) versus weight-based (6-mg/kg) doses are used to treat IFI.

A single-center retrospective cohort study found inadequate doses of fluconazole were used in 16% of patients (n=356) and was an independent determinant of mortality (Labelle 2008). The DALI study, a multi-center point-prevalence study looking at pharmacokinetic-pharmacodynamic target attainment of fluconazole in critically patients, found that 33% of fluconazole patients (n=15) did not achieve the desired AUC/MIC ratio of 100 or greater. This study also found the median dose needed to achieve this goal was 5 mg/kg (Sinnollareddy 2015).

Obesity is another factor altering the pharmacokinetics of antifungal agents. Obese patients tend to have alterations in volume of distribution. Fat mass, as well as lean body mass are increased in obese patients, whereas blood flow to adipose tissue is reduced. These patients also can have reduced hepatic blood flow and metabolism caused by fatty liver infiltration. Specifically, CYP3A4 metabolism has been shown to be reduced in obese patients. Renal clearance tends to increase as lean body mass increases; therefore, obese patients tend to have enhanced renal clearance of drugs. Only a few studies have specifically investigated antifungal agent pharmacokinetics in obese patients. The general consensus is that amphotericin products do not distribute into adipose tissue and should be dosed based on lean body weight; fluconazole should be dosed on total body weight at the higher end of the dose range; voriconazole and posaconazole should be dosed on lean body weight; and dose increases of 20%–50% should be considered for the echinocandins.

Therapies on the Horizon

The introduction of extended-spectrum azoles and the echinocandins have significantly improved the treatment options for IFIs. Despite these advances, only three unique classes of antifungal agents are currently available. All have considerable limitations, toxicities, and drug interactions. Furthermore, clinical outcomes in patients with fungal infections remain poor, and resistance to current therapies is increasing. As rates of fungal infections are mounting with the increased use of immunosuppressing therapies, new agents with unique or synergistic mechanisms of action are needed. Unfortunately, several challenges exist in finding new drug targets specific to fungal pathogens, as well as discovering new assays that are better at detecting growth inhibition and activity against fungal biofilms. With only a few new drugs close to being marketed, antifungal drug development may not keep up with clinical demands for these agents.

In March 2015, the FDA approved isavuconazonium sulfate, an azole antifungal, for the treatment of adult patients with IA and mucormycosis. Isavuconazonium is a prodrug that is rapidly hydrolyzed to isavuconazole, the active drug that offers the advantage of once-daily dosing. The efficacy of isavuconazonium has been shown in clinical trials to be noninferior to voriconazole in the treatment of IA. It was also shown to be effective in noncomparative trials for the treatment of primary mucormycosis or mucor infections refractory or intolerant to other agents. Limitations to the mucor data include a small number of patients analyzed with no comparison group, as well as finding the MICs for some common Mucorales may surpass plasma levels achieved with currently recommended dosing.

It is unknown how isavuconazole compares with either amphotericin B or posaconazole for the treatment of mucormycosis, but mortality rates appeared to be similar based on retrospective comparisons to posaconazole salvage studies and case-control studies with amphotericin B. The spectrum of activity also includes *Candida* spp. such as *C. glabrata* (including fluconazole-resistant strains) and *C. krusei*, as well as *Cryptococcus*, *Histoplasmosis*, *Blastomycoses*, and *Coccidioides*. Isavuconazole is available in an intravenous formulation that does not contain the cyclodextrin excipient, although it does require an in-line filter. An oral formulation is also available, but these capsules cannot be opened and administered via a nasogastric tube.

Like other azoles, isavuconazole is a substrate of CYP3A and a moderate inhibitor of CYP3A4. Reported drug-drug interactions appear less significant with isavuconazole than with other azoles, although the data were obtained using doses lower than currently recommended. Further investigations as well as clinical experience are awaited and caution should be used when co-administering with drugs known to interact via CYP3A. Therefore, close TDM of concomitant cyclosporine, tacrolimus, and sirolimus is warranted, but empiric dose adjustments are not currently recommended. Administration of isavuconazonium with strong CYP3A inhibitors and inducers is contraindicated.

Compared with voriconazole, isavuconazole appears to be better tolerated with a lower incidence of visual disturbances and hepatotoxicity. Adverse effects are mostly GI (nausea, vomiting, diarrhea, constipation), but hypokalemia, liver toxicity, shortened QT interval, and infusion reactions have been seen in clinical trials. The long half-life of this drug may make managing drug interactions and adverse effects challenging because of the prolonged toxicities and delays in starting therapy until the drug has been fully eliminated.

An additional drug that inhibits β-(1,3)-glucan synthase under development is biafungin (CD101), a novel long-acting echinocandin. This agent is being developed for the prevention and treatment of candidiasis including infections caused

by resistant species. Its long half-life may allow for a once-weekly dose that could prevent the need to switch agents and also allow for earlier discharge.

Several antifungal agents are currently in development that target specific components of the fungal cell wall such as β-(1,6)-glucan synthase and glycosylphosphatidylinositol-linked protein acyltransferase, as well as leucyl tRNA synthetase and poly(A) polymerase. However, because of the slow pace of drug development, these agents are not likely to be soon available.

CONCENTRATION MONITORING

The use of TDM to guide antifungal therapy is becoming increasingly common. Although routine monitoring is not recommended for all patients, there are several circumstances in which TDM may be useful in the critically ill (Box 1-2). The challenges with concentration monitoring include differences in available assays in terms of sensitivity and specificity, increased expenses, long turnaround times, and the difficulty in determining the effect on clinical outcomes. It is important to remember the recommended therapeutic ranges are based on small numbers of patients often stemming from populations that may not be similar to the individual patient in the ICU. Therefore, knowing the MIC of the organism, using clinical judgment, and adequately monitoring clinical response to therapy must be used in conjunction with serum drug concentration data. Concentration monitoring should not take precedence over changing antifungal agents in someone who is clearly being failed by therapy.

Antifungal concentration monitoring is mainly limited to the triazoles that cover mold pathogens (i.e., itraconazole, voriconazole, and posaconazole) and flucytosine. The goal trough concentrations, timing of serum sampling, and recommendations for dose adjustments for these agents are listed in Table 1-5. There is no role in monitoring concentrations of amphotericin B (despite its toxicities) or the echinocandins. Fluconazole concentration monitoring is also not typically recommended; however, it may be considered when the MIC of the pathogen is increased, when treating CNS disease, or in patients requiring renal replacement therapy. Recommendations for isavuconazole TDM have not been clearly defined. It has excellent oral bioavailability, linear kinetics, and very little intersubject variability in concentrations; therefore, TDM is not likely to be necessary.

Itraconazole displays non-linear pharmacokinetics with significant variability in oral absorption because of formulation differences (30% higher AUC with the oral solution vs. capsules), food, and gastric pH. Therefore, TDM can be recommended for most patients receiving this antifungal to ensure adequate absorption is achieved. The strongest evidence to support TDM of itraconazole comes from studies looking at exposure-response relationships in the prevention of fungal disease in patients with immunocompromise. The recommendations for therapeutic treatment concentrations are mostly extrapolated from these data, making it difficult to interpret. The guidelines from the British Society of Medical Mycology (BSMM) recommend a concentration greater than 0.5 mg/L for both prophylaxis and treatment; however, the limited evidence available indicates a target trough concentration of at least 1 mg/L for treatment regimens may be preferred.

Voriconazole also exhibits non-linear pharmacokinetic variability in adult patients, mainly because of saturable hepatic metabolism and genetic polymorphisms of the CYP2C19 hepatic enzyme. Evidence also suggests that the FDA-approved fixed non–weight-based oral doses of voriconazole may be inadequate to achieve effective serum concentrations. This issue is of particular concern in obese patients and those with active disease, for whom the maximal recommended dose may need to be exceeded. Children have linear nonsaturable pharmacokinetics with voriconazole (requiring much higher weight-based doses) as well as lower oral bioavailability.

There is a clear exposure-response relationship demonstrated with voriconazole in both pre-clinical and clinical trials. Therefore, TDM can be considered in patients at high risk for genetic polymorphism (i.e., those of Asian descent), those receiving drugs known to alter voriconazole metabolism, those transitioning to oral therapy, and in pediatric patients. Again, the BSMM recommends similar target trough concentrations for both treatment and prophylaxis because most of the literature exploring exposure-response relationships comes from treatment doses. However, there is limited evidence to suggest a target trough of 0.5 mg/L in the prophylaxis of fungal infections is adequate.

Because of the transient nature of the visual disturbances associated with voriconazole and the rare reports of neurologic and liver toxicity seen with typical doses, TDM for the

Box 1-2. When to Consider Concentration Monitoring

- Age extremes
- Compliance questionable
- Concomitant use with acid suppressing therapy
- Drug interactions, significant
- Extensive, bulky, or disseminated infection (e.g., CNS, mediastinal)
- Malabsorption
- Obesity
- Organ dysfunction
- Prophylaxis in high-risk patients
- Renal replacement therapy
- Use of extracorporeal membrane oxygenation or cardiopulmonary bypass

Information from Ashbee HR. Therapeutic drug monitoring of antifungal agents: guidelines from the British Society of Medical Mycology. J Antimicrob Chemother 2014;69:1162-76.

Table 1-5. Recommendations for Therapeutic Drug Monitoring

Drug	Minimum Target Concentrations[a]	Timing of Concentration[b]	Concentrations Associated with Toxicity	Strategies to Increase Low Concentrations
Itraconazole	P: 0.5 mg/L T: 0.6–1 mg/L	7–14 days	> 17 mg/L[c]	Change to solution Avoid acid suppressants with capsules Take solution in fasting state Increase dose from 200 mg twice daily to 300 mg twice daily
Voriconazole	P: > 1 mg/L T: > 1 mg/L Trough:MIC of 2–5	Within 7 days[d]	> 5.5 mg/L	Increase dose: IV: up to 6 mg/kg twice daily PO: up to 300 mg twice daily
Posaconazole[e]	P: 0.35 mg/L P: > 0.7 mg/L T: > 1 mg/L	At 48 hours Within 7 days	Unknown	Increase total daily dose to 800 mg Administer total daily dose divided four times daily Switch to the delayed-release tablets Avoid acid suppressants Take with food or high-fat supplement
Flucytosine	T: Peak 20–40 mg/L	Within 72 hours	Peak >100 mg/L	Increase dose by 50%, use caution due to toxicity

[a]Trough concentrations measured using high performance liquid chromatography (HPLC)/mass spectrometry unless otherwise specified.

[b]Time listed is the number of days after the initiation of therapy.

[c]Concentration measured with bioassay, would expect 5-fold lower concentration with HPLC/mass spectrometry.

[d]Repeat level may be necessary because of fluctuations in concentrations due to Michaelis-Menten kinetics.

[e]Recommendations are for oral solution only.

IV = intravenous; P = prophylaxis; PO = oral; T = treatment.

Information from Ashbee HR. Therapeutic drug monitoring of antifungal agents: guidelines from the British Society of Medical Mycology. J Antimicrob Chemother 2014;69:1162-76.

sole reason of minimizing toxicity cannot be recommended. It can be considered in patients demonstrating signs of toxicity, especially if multiple reasons for this toxicity exist (to rule out a drug effect) or in patients receiving doses higher than recommended by the manufacturer. In patients not displaying signs of toxicity with trough concentrations greater than 5 mg/L, dose reductions may not be necessary but should be assessed case-by-case considering the status of the underlying infection.

Posaconazole TDM is recommended in most patients receiving the suspension because of poor bioavailability from saturable absorption and reduced absorption in the setting of mucositis, graft-versus-host disease, the concomitant administration with acid-suppressing therapies, or administration without a high-fat meal. Concentrations have been found to be suboptimal in 50% of patients receiving posaconazole suspension for fungal prophylaxis. Target trough concentrations in prophylactic studies have varied from 0.5 to 0.7 mg/L, but have all consistently shown a trend towards a better likelihood of response with increased drug exposure. Similar trends for a better response with increased drug exposure have been seen in studies for the treatment of aspergillosis. The MIC breakpoints recently set for posaconazole susceptibility to *Aspergillus* spp. are only considered valid if target serum concentrations have been achieved. Most studies indicate adequate exposure of posaconazole from the delayed-release tablets and the intravenous formulation; therefore, routine TDM with these preparations is not recommended at this time unless toxicity, treatment failure, or breakthrough infection is suspected.

Flucytosine is a pyrimidine analog commonly used with amphotericin B to treat cryptococcal meningitis. Implications for TDM include its toxicity profile, significant intra- and inter-patient pharmacokinetic variability, dependence on renal elimination where nephrotoxicity is common, and its risk of developing resistance. Evidence from pharmacodynamics studies indicates a strong exposure-toxicity relationship with a higher incidence of bone marrow suppression and hepatotoxicity seen at peak concentrations exceeding 100 mg/L. Although historically flucytosine

dosing has targeted a peak concentration to limit toxicity, the correlation between flucytosine serum concentration and efficacy is less clear, and even lower targets may be adequate. Maintaining concentrations above the MIC for at least 50% of the interval has been associated with improved clinical outcomes in the treatment of *Candida* infections and may prevent the emergence of resistance. Unfortunately, even less is known about target concentrations for cryptococcal disease or in combination with amphotericin B, where flucytosine is more commonly used. It is recommended that peak concentrations be performed to prevent toxicity and minimize the risk of resistance.

For all antifungal agents, it is important to know what assay was used to determine drug concentrations. Bioassay is still commonly employed in some commercial laboratories and can overestimate drug exposure, particularly when combination antifungal therapy is used. Interpretation should also take into consideration past use of agents with long terminal half-lives. For example, if bioassay is being used to ensure adequate concentrations of an oral agent, activity from a previously discontinued amphotericin B product may be contributing to antifungal activity, resulting in false security in the azole concentration.

Adjusting doses for sub- or supra-therapeutic concentrations should be done with caution. For recommendations on increasing doses for sub-therapeutic concentrations after assessing for compliance and drug interactions, see Table 1-5. Guidance on how to adjust for supra-therapeutic concentrations is less clear and cannot always be recommended unless signs of toxicity are present. One exception to this approach is with flucytosine, because toxicity is more common and the exposure-toxicity relationship is clear. Another case may be with voriconazole, for which it is recommended to decrease the dose by 50%, but, because of Michaelis-Menten kinetics, smaller adjustments may be necessary.

ANTIFUNGAL STEWARDSHIP

Pharmacists are recognized as key members of antimicrobial stewardship teams and have an important role in optimizing antifungal use in the ICU. Recent advances in diagnostic tools, susceptibility testing, and newly approved

Patient Care Scenario

A 67-year-old white man with acute myeloid leukemia after bone marrow transplant is on high-flow oxygen in the medical ICU and receiving voriconazole 4 mg/kg intravenous twice daily for pulmonary Aspergillus. His oxygenation has not been improving, so the ICU team ordered a voriconazole concentration.

Day of therapy	5
Voriconazole trough concentration	1.2 mg/L

The ICU team asks for recommendations on how to interpret this concentration and adjust his voriconazole dose. At this time the patient's clinical condition has not improved and he is close to needing intubation. He is not displaying any signs of voriconazole toxicity.

ANSWER

According to the guidelines from the British Society of Medical Mycology, a voriconazole trough concentration more than 1 mg/L taken within 7 days of treatment is considered an adequate serum concentration for treatment of invasive fungal infections. Therefore, this level taken on day 5 of therapy should be representative of a therapeutic steady state concentration. However, because of the non-linear pharmacokinetics and lack of data strongly correlating drug concentration and clinical outcome, it is important to interpret this level also based on the clinical picture of the patient. The reasons for this patient to have concentrations on the lower side of therapeutic include a genetic polymorphism of CYP-2C19 and his history of bone marrow transplant (this population tends to have lower concentrations than healthy volunteers).There is evidence to suggest that trough concentrations less than 2 mg/L may be associated with clinical failure in patients with invasive aspergillosis. Therefore it would be reasonable to increase the dosage to 6 mg/kg intravenous twice daily and monitor for signs of toxicity. It would also be reasonable to repeat another trough concentration in 5 to 7 days because of the non-linear kinetics. If the clinical picture worsens significantly, it may be time to consider alternate or combination therapy for this patient.

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agents highlight the complexity in managing IFIs and the need for a medical team member with expertise in antifungal agents be involved. The ICU pharmacist is the most qualified member of the health care team to optimize antifungal therapy by identifying appropriate patients in need of antifungals, by ensuring appropriate choice and dose of drug based on susceptibilities and TDM, by identifying drug interactions and adverse effects, and by helping to develop guidelines focused on minimizing overuse to prevent resistance and reduce health care costs.

CONCLUSION

Fungal infections are associated with considerable morbidity and mortality in ICU patients even when appropriately treated. Delays in therapy can negatively impact outcomes and increase health-care costs. Several challenges exist in identifying patients at risk of these infections and in achieving an accurate diagnosis. Furthermore, antifungal pharmacotherapy has become very complex with the introduction of new agents, susceptibility testing, and TDM. Clinical pharmacists can play a huge role in optimizing therapy and help develop institutional protocols and algorithms to better manage these patients.

Practice Points

When considering empiric and definitive antifungal therapy in the critically ill, several factors should be taken into consideration:

- **What is the overall risk of invasive fungal disease?**
  - **Clinical prediction scores can be used to help rule out infection.**
  - **Clinical prediction scores can be used in addition to the clinical status of the patient, cultures, and other diagnostic tests to help rule in the likelihood of infection.**
- **Should a rapid diagnostic test be sent?**
  - **This approach is based on the availability and turnaround time of the test as well as the presence of any factors that may lead to a false-positive or –negative result.**
  - **If the test result is negative, then it could be useful to help discontinue unnecessary antifungals.**
- **Are positive cultures true infection versus colonization?**
  - ***Candida* in the blood is usually reflective of true infection, whereas *Candida* in the sputum or urine is most likely contamination.**
- **What are the common pathogens and susceptibilities seen at your institution?**
  - **Choice of drug will depend on the prevalence of non-*albicans* or fluconazole resistant species.**
- **What patient specific factors exist that may influence choice of drug?**
  - **Consideration of these factors is needed: drug interactions, organ dysfunction, severity of illness, source/eye involvement, oral route/diet, obesity, and potential for polymorphisms.**

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Self-Assessment Questions

Questions 1–4 pertain to the following case.

P.T. is a 56-year-old man who is transferred to the ICU and intubated for hypoxic respiratory failure 21 days after a bone marrow transplant for acute myeloid leukemia. He was found to have pulmonary aspergillosis and is being treated with voriconazole 300 mg intravenous twice daily and caspofungin 50 mg intravenous daily. P.T. has a history of hypertension and gastroesophageal reflux disease, and he has developed acute kidney injury with an estimated CrCl of 40 mL/minute as well as graft versus host disease of the skin and gut. During the infusion of caspofungin the nurse notes that P.T. has become febrile, flushed, and has some facial swelling.

1. Which one of the following toxicities is P.T. most likely experiencing?
   A. Anaphylactic reaction to caspofungin; stop the infusion and administer epinephrine.
   B. Infusion reaction to caspofungin; discontinue caspofungin.
   C. Histamine-mediated reaction to caspofungin; slow the infusion rate.
   D. Accumulation of cyclodextrin in the intravenous voriconazole formulation; discontinue voriconazole.
2. In the next 72 hours, P.T. does not show much clinical improvement in respiratory function. His kidney function is worsening, and he is having high residuals from his tube feeds. Despite this, the oncology fellow would like to switch the voriconazole from intravenous to oral out of concern for cyclodextrin accumulation. Which one of the following is best to recommend for P.T.?
   A. Switch the voriconazole to oral because the risks of cyclodextrin outweigh the benefit of intravenous therapy.
   B. Continue with intravenous therapy because the risk of toxicity from cyclodextrin is theoretical and the patient is unlikely to absorb oral therapy.
   C. Change to liposomal amphotericin B because of concern for toxicity and lack of oral absorption.
   D. Discontinue voriconazole and continue caspofungin monotherapy as the toxicity being seen is from voriconazole itself.
3. P.T.'s graft versus host disease (GVHD) is nonresponsive to steroid treatment. The team is contemplating whether an IL-2 receptor antibody (e.g., etanercept), a mammalian target of rapamycin (mTOR) inhibitor (sirolimus), or therapy with daclizumab would be best to treat steroid refractory disease. Which one of the following is best to recommend for P.T.?
   A. Avoid sirolimus because of significant drug-drug interaction with voriconazole.
   B. Avoid etanercept because of the treatment for active fungal infection.
   C. Avoid daclizumab because monoclonal antibodies complicate identification of the cause of the patient's flushing and facial swelling.
   D. Avoid all of the above therapies because they will result in accumulation of caspofungin
4. P.T. has now had 7 days of combination antifungal treatment, and the team is debating the need for antifungal therapeutic drug monitoring (TDM). They are considering converting to oral voriconazole in the next several days. Which one of the following is the most compelling reason to avoid TDM in B.L. at this time?
   A. It is too early to determine whether or not he is responding to treatment.
   B. High performance liquid chromatography (HPLC) will not be able to detect differences between caspofungin and voriconazole concentrations.
   C. The patient demonstrates no signs of toxicity and will be converted to oral therapy before test results are available (7–10 days at your institution).
   D. There is no need for TDM when using the intravenous formulation of voriconazole.

Questions 5–9 pertain to the following case.

B.L. is a 37-year-old man admitted to the trauma ICU after a motor vehicle crash. He sustained multiple fractures and a splenic laceration and is currently intubated after repair of a right pelvic fracture. B.L. has a right-sided chest tube in place for pneumothorax, as well as a Foley catheter that was placed at admission. He had no contributory medical history. His current drug regimen includes ampicillin/sulbactam for prophylaxis secondary to facial fractures, hydromorphone PCA, docusate, senna, and enteral feeding supplements.

5. Forty-eight hours after B.L. arrived in the ICU, surveillance cultures were obtained. They were notable for yeast in the sputum and urine (taken from Foley collection bag) but not the other two sites that were cultured. Which one of the following is best to recommend for B.L.?
   A. Initiate fluconazole 400 mg daily.
   B. Initiate nystatin five times a day.
   C. Initiate daily β-D-glucan testing.
   D. Monitor for signs and symptoms of infection.
6. It is now day 10 of B.L.'s hospital admission. Overnight, he has become febrile (39.7°C) and hypotensive. His antibacterial therapy is being broadened to piperacillin/tazobactam and vancomycin. Blood cultures were drawn peripherally and through his central line. Which one

of the following is best to recommend regarding B.L.'s antifungal regimen?

A. Add a galactomannan test to the above ordered cultures.
B. Continue without change until initial culture results.
C. Change treatment to lipid amphotericin B product at 5 mg/kg every 24 hours.
D. Initiate amphotericin B bladder irrigation daily.

7. Twenty-four hours later, B.L.'s cultures return; both peripheral blood and cultures obtained through the catheter are positive for yeast. The patient remains febrile. Which one of the following is best to recommend as empiric treatment for B.L.'s fungemia?

A. Fluconazole 800 mg intravenous every 24 hours.
B. Amphotericin B 0.5 mg/kg intravenous every 24 hours.
C. Micafungin 100 mg intravenous every 24 hours.
D. Micafungin 50 mg intravenous every 24 hours.

8. Twenty-four hours later, the microbiology laboratory reports that B.L.'s culture is positive for *Candida albicans*. Antifungal susceptibility testing is not standard at your institution, and a send-out laboratory test has a 5–7 day turnaround time. Which one of the following is best to recommend for B.L.?

A. Continue/initiate micafungin 100 mg intravenous every 24 hours.
B. Convert to oral voriconazole 200 mg every 12 hours.
C. Continue/initiate fluconazole 800 mg intravenous every 24 hours.
D. Call the laboratory to request susceptibility testing.

9. B.L. is now in day 5 of treatment; he is afebrile, and blood cultures obtained at 48 hours of treatment remain negative. His central line has been replaced over a guide wire. He is otherwise clinically stable and being weaned from the vent. Which one of the following treatment durations is recommended for B.L.'s episode of candidemia?

A. Additional 14 days of therapy.
B. Additional 7 days of therapy.
C. Additional 9 days of therapy.
D. Additional 11 days of therapy.

Questions 10 and 11 pertain to the following case.

The antibiotic stewardship committee at HealthHome Hospital has recently begun to focus on antifungal stewardship. You are invited to a meeting to discuss proposed new diagnostic technologies for HealthHome Hospital.

10. Which one of the following points is the most compelling to present to the HealthHome committee, especially for patients in the ICU?

A. PNA FISH should be performed to allow earlier initiation of appropriate antifungal therapy; use can be justified based on decreased echinocandin therapy.
B. Beta-glucan should be added to facilitate shorter courses of antifungal agents; use can be justified based on decreased overall antifungal therapy.
C. Galactomannan testing should be added to allow more rapid diagnosis of aspergillosis; use can be justified based on decreased need for voriconazole prophylaxis.
D. Mannan/anti-mannan testing should be added to allow earlier initiation of appropriate antifungal therapy; use can be justified based on decreased echinocandin therapy.

11. In lieu of any of the new diagnostic technologies discussed, the HealthHome committee decided to add susceptibility testing at the local level. You are asked to create a guideline for preemptive therapy for invasive fungal infections in the ICU. The reference laboratory has supplied the following information for the past 100 isolates of *Candida* spp at HealthHome Hospital:

Organism	Number of isolates	% susceptible to fluconazole
C albicans	51	80
C parapsilosis	20	98
C glabrata	13	60
C krusei	6	-
C tropicalis	10	74

Which one of the following drugs would be best to use for HealthHome patients who qualify for preemptive antifungal therapy per your guideline?

A. Lipid amphotericin B
B. Caspofungin
C. Fluconazole
D. Flucytosine

12. A 35-year-old woman is receiving home TPN therapy. She presents to the ED septic and is being admitted to the medical ICU. The team wishes to cover likely fungal pathogens and asks your advice. Which one of the following drugs is best to recommend for this patient's empiric antifungal therapy?

A. Caspofungin
B. Amphotericin B
C. Amphotericin B lipid complex
D. Fluconazole

13. The pharmacy and therapeutics committee is reviewing drugs newly approved by the FDA. They have interest in reviewing isavuconazonium. Which one of the following is the best guidance to give to the committee regarding isavuconazonium?

A. It has a similar spectrum to voriconazole with possible enhanced activity against Zygomycetes but fewer adverse events.

B. It has a spectrum similar to posaconazole but must be administered more frequently.
C. It has a slightly broader spectrum than fluconazole but more concerns regarding administration with acid suppressive agents.
D. It is similar in spectrum to itraconazole but lacks an intravenous formulation.

14. A 56-year-old woman is receiving treatment for influenza in the medical ICU. She is intubated and sedated. Her medical history includes Crohn disease, hypertension, and hyperlipidemia. Her current drugs include fentanyl and midazolam continuous infusions, infliximab 5 mg/kg (monthly), atorvastatin 40 mg daily, valsartan 40 mg daily, and pantoprazole 40 mg every 12 hours. On day 2 of her hospital admission, she is noted to have a new patchy infiltrate in the right lower lobe on routine chest radiography. A sputum culture reveals *Candida* spp. but nothing else grows. The patient is running a low-grade fever (38.1°C) and has a slightly elevated WBC (6.8 x 10^3 cells/mm^3). Which one of the following is best to recommend regarding antifungal therapy for potential candidiasis for this patient?

A. Initiate fluconazole 800 mg daily.
B. Initiate voriconazole 4 mg/kg every 12 hours.
C. Do not treat, administer nystatin to decontaminate oral cavity.
D. Do not treat.

Questions 15 and 16 pertain to the following case.

Z.K. is a 45-year-old man admitted to the surgical ICU after a gunshot wound to the abdomen. On day 8 post-surgery he remains intubated and is now febrile (40°C). His condition had been improving but he is now septic, requiring pressors. For the past 3 days Z.K. has received anti-bacterial therapy with ciprofloxacin for a positive urine culture with *E. coli*, and he continues to have a urinary catheter in place.

15. According to which clinical prediction score would Z.K. meet criteria for early antifungal therapy based on a > 75% sensitivity?

A. Dupont score
B. *Candida* score
C. Ostrosky rule
D. Modified Ostrosky rule

16. Cultures are obtained from Z.K. and empiric antifungal therapy is started with fluconazole 400 mg daily because of an ongoing echinocandin shortage at your hospital. Blood cultures are subsequently reported positive for *C. glabrata.* Susceptibility testing is performed and the fluconazole MIC is 16. Which of the following is best to recommend for Z.K.'s antifungal treatment?

A. Continue fluconazole but increase dose to 800 mg daily.
B. Continue fluconazole but obtain drug concentrations after 5–7 days of therapy.
C. Change antifungal therapy to voriconazole.
D. Change antifungal therapy to a lipid preparation of amphotericin B.

Questions 17–19 pertain to the following case.

M.R., a 45-year-old woman with acute myelogenous leukemia (AML), recently visited family members in Arizona. Now she is admitted for her third cycle of induction chemotherapy. Over the past 2 months M.R. has developed significant neuropathic pain; she recently begun carbamazepine but otherwise her medications are unchanged. She receives voriconazole 200 mg every 12 hours as prophylaxis with each cycle. On day 7 of hospital admission, M.R. is transferred to the ICU for mental status changes and acute hypoxia. She is started on empiric therapy for pneumonia (piperacillin/tazobactam and vancomycin), and her antifungal therapy is continued. Chest CT reveals new nodules. The primary team wishes to obtain rapid fungal diagnostic testing.

17. Which one of the following tests would best determine whether M.R. has developed fungal infection?

A. PCR of a blood sample
B. PCR of BAL sample
C. Galactomannan of blood sample
D. Galactomannan of BAL sample

18. M.R.'s health care team is worried this may be a breakthrough infection on voriconazole. Which of the following puts M.R. at greatest risk of breakthrough fungal disease?

A. Recent travel to Arizona
B. Recent chemotherapy
C. Failure of voriconazole prophylaxis due to drug interaction
D. Duration of stay in the ICU

19. Which one of the following is the most compelling reason to modify M.R.'s antifungal therapy?

A. Development of breakthrough fungal infection on treatment
B. A voriconazole concentration of 0.5 mg/L
C. Concerns for carbamazepine/voriconazole drug-drug interaction
D. Need to initiate combination antifungal treatment

20. Which one of the following would best monitor to predict efficacy of voriconazole in a patient being treated for invasive aspergillosis?

A. Voriconazole peak concentrations
B. Voriconazole trough concentrations
C. Galactomannan
D. Voriconazole MIC

Learner Chapter Evaluation: Fungal Infections in the ICU.

As you take the posttest for this chapter, also evaluate the material's quality and usefulness, as well as the achievement of learning objectives. Rate each item using this 5-point scale:

- Strongly agree
- Agree
- Neutral
- Disagree
- Strongly disagree

1. The content of the chapter met my educational needs.
2. The content of the chapter satisfied my expectations.
3. The author presented the chapter content effectively.
4. The content of the chapter was relevant to my practice and presented at the appropriate depth and scope.
5. The content of the chapter was objective and balanced.
6. The content of the chapter is free of bias, promotion, or advertisement of commercial products.
7. The content of the chapter was useful to me.
8. The teaching and learning methods used in the chapter were effective.
9. The active learning methods used in the chapter were effective.
10. The learning assessment activities used in the chapter were effective.
11. The chapter was effective overall.

Use the 5-point scale to indicate whether this chapter prepared you to accomplish the following learning objectives:

12. Classify a critically ill patient's risk of invasive fungal infection.
13. Construct an algorithm for routine surveillance of invasive fungal infections in the ICU.
14. Distinguish key considerations for a reasonable prophylactic, preemptive, or empiric antifungal therapy regimen for a patient in the ICU.
15. Justify antifungal treatment algorithms designed for the ICU based on current evidence.
16. Evaluate the newer antifungal agents and their relative advantages and disadvantages in the ICU setting.
17. Please provide any specific comments related to any perceptions of bias, promotion, or advertisement of commercial products.
18. Please expand on any of your above responses, and/or provide any additional comments regarding this chapter:

Antimicrobial Management of HAP/VAP

By Martin J. Ohlinger, Pharm.D., FCCM

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LEARNING OBJECTIVES

1. Evaluate recent literature and current guidelines on the risk factors and management of hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP).
2. Develop measures to prevent HAP and VAP, as well as complications associated with prolonged mechanical ventilation in the ICU.
3. Using key pharmacokinetic and pharmacodynamic principles, as well as individual patient information, design an appropriate regimen for the management of HAP/VAP.
4. Distinguish common multidrug resistant HAP/VAP pathogens and recommend potential antimicrobials for treatment.

ABBREVIATIONS IN THIS CHAPTER

ATS	American Thoracic Society
CPIS	Clinical Pulmonary Infection Score
ESBL	Extended-spectrum β-lactamase
HAP	Hospital-acquired pneumonia
HCAP	Health care–associated pneumonia
IDSA	Infectious Diseases Society of America
KPC	*Klebsiella pneumoniae* carbapenemase
MDR	Multidrug resistant
MRSA	Methicillin-resistant *Staphylococcus aureus*
SDD	Selective decontamination of the digestive tract
SOD	Selective oropharyngeal decontamination
VAP	Ventilator-associated pneumonia

INTRODUCTION

Health care–associated pneumonia (HCAP), hospital-acquired pneumonia (HAP), and ventilator-associated pneumonia (VAP) are significant infectious disease problems in the management of the critically ill or injured patient. The term *health care–associated pneumonia* is defined as pneumonia occurring in a patient with a recent history of hospitalization (within 90 days); a patient residing in a long-term care facility or attending a hospital or hemodialysis clinic; or a patient who has received intravenous antimicrobial therapy, chemotherapy, or wound care within the past 30 days. *Hospital-acquired pneumonia* is defined as pneumonia occurring 48 hours or more after admission to a hospital. *Ventilator-acquired pneumonia* is defined as pneumonia occurring more than 48–72 hours after endotracheal intubation (ATS/IDSA 2005).

Ventilator-acquired pneumonia accounts for about one-half of all HAP and is the most common nosocomial infection in patients receiving mechanical ventilation (Vincent 1995). Depending on the definition and diagnosis used for VAP, rates are 1.2–8.5 per 1000 patient-ventilator days (Kalanuria 2014; Hunter 2012). Despite an increased awareness and a multitude of resources directed toward prevention and management, the attributable morbidity and mortality from VAP remains high. One study showed an increase in average ICU length of stay of 4.3 days in patients with VAP, and an increased relative risk of mortality of 32.3% compared with patients without VAP (Heyland 1999). Mortality rates for patients with VAP may be at least 2-fold higher with concurrent bacteremia (Siempos

2010; Agbaht 2007). The frequent need for intubation and mechanical ventilation, as well as exposure to nosocomial pathogens and antimicrobial resistance, continue to make the management HAP and VAP difficult.

Typically VAP is caused by microaspiration of the upper airway secretions. Efforts to prevent microaspiration of contaminated secretions (e.g., improved endotracheal tube technology, various decontamination techniques) have had limited success. Risk factors for developing VAP include endotracheal intubation, enteral feeding, oversedation, re-intubation, and supine positioning (Kalanuria 2014; Hunter 2012). Similarly, HCAP and HAP are also caused by microaspiration. The differences between HCAP/HAP and VAP are simply based on the location of the patient and the timing of onset of infection.

The definition, diagnosis, and surveillance of VAP have changed significantly over time. Criteria continue to evolve, but the sensitivity and specificity of these criteria in predicting actual cases of VAP remain low, frustrating both clinicians and researchers. A recent Critical Care Societies Collaborative task force suggested moving toward surveillance of ventilator-associated events versus VAP alone (CCSC 2015). Examples of ventilator-associated events (in addition to VAP) include worsening oxygenation and increasing positive end expiratory pressure (CDC 2015).

BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:

- General understanding of the pathophysiology that leads to HAP and VAP
- Definition and diagnosis of HAP and VAP
- Pathogens commonly implicated in HAP and VAP
- Parenteral antimicrobials commonly used in the treatment of pneumonia in the acute care patient

ADDITIONAL READINGS

The following free resources have additional background information on this topic:

- American Thoracic Society. Guidelines for the Management of Adults with Hospital-acquired, Ventilator-associated, and Healthcare-associated Pneumonia
- File TM Jr. Treatment of hospital-acquired, ventilator-associated, and healthcare-associated pneumonia in adults
- Institute for Healthcare Improvement. Ventilator-Associated Pneumonia

GUIDELINES

Guidelines for the management of HCAP, HAP, and VAP in the United States were jointly published by the American Thoracic Society (ATS) and the Infectious Diseases Society of America (IDSA) in 2005. International guidelines have been published by the Association of Medical Microbiology and Infectious Disease Canada, the Brazilian Sociedade Brasileira de Pneumologia e Tisiologia, British Society of Antimicrobial Chemotherapy, Japanese Respiratory Society, Latin American Thoracic Society, Portuguese Society of Pulmonology and Intensive Care Society, and the South African Thoracic Society. These international guidelines were summarized in a review article (File 2010) and do not differ significantly from the ATS/IDSA guidelines.

Although evidence-based and well-accepted, much has changed in the management of HAP and VAP since the publication of many of these guidelines. In this chapter, unless otherwise indicated, any reference to guidelines will be to the ATS/IDSA guidelines.

PREVENTION

Whereas antimicrobials are often needed to treat a suspected or definitive case of HAP or VAP, much effort has been directed toward prevention of HAP and VAP. One approach has been the use of a ventilator bundle. A concept developed by the Institute for Healthcare Improvement, the bundle is a set of practice components designed to synergistically improve patient outcomes. The ventilator bundle has been shown to decrease the risk of VAP as well as other potential complications related to mechanical ventilation (Resar 2005). The typical ventilator bundle consists of elevation of the head of the bed, daily sedation vacation and assessment of readiness to extubate, daily oral care with chlorhexidine gluconate, stress ulcer prophylaxis, and deep venous thrombosis prophylaxis (Table 2-1).

Selective decontamination of the digestive tract (SDD) is typically described as the use of (1) a short course (e.g., 3 days) of a parenteral antimicrobial to prevent early primary endogenous infections; (2) oropharyngeal and enteral antimicrobials administered in the throat and gut throughout the ICU admission to prevent late secondary infections; (3) good hygiene to control transmission of potential pathogens; and (4) surveillance microbial samples of the throat and rectum to monitor the efficacy of the treatment.

A similar strategy is selective oropharyngeal decontamination (SOD). Both SDD and SOD have been studied for the prevention of VAP, with mixed results on outcomes such as infection rates, changes in microbial resistance, and mortality. A review of 53 randomized trials and six meta-analyses compared SDD with standard care and reported outcomes in favor of SDD (van Saene 2003). Nonetheless, full SDD is rarely used for reasons including (1) it is extremely labor intensive; (2) the potential for antimicrobial resistance

Table 2-1. Components of a Ventilator Bundle

Component	Purpose	Implementation	Pharmacotherapy	Special Notes/Pharmacy Implications
Elevate HOB to 30°–45°	Reduce the VAP risk by reducing the risk of aspiration	Unless contraindicated, HOB should be elevated to 30°. If contraindicated, reverse Trendelenburg position can be used.	N/A	Contraindications/precautions include: • Severe hypotension • Unstable spine • Pelvic fracture • Intra-aortic balloon pump • Morbid obesity • Prone position
Daily SAT/SBT	Assess for readiness to extubate Assess level of consciousness by lightening or stopping sedation	Physician, pharmacy, nursing, and respiratory therapy work together to: Adjust sedation appropriately Place patient on spontaneous mode of ventilation	N/A	Pharmacologic contraindications/precautions include: • Patients receiving NMBAs • Patients requiring deep sedation Nonpharmacologic contraindications/precautions include: • Patients requiring full ventilator support/unable to breathe spontaneously • Inadequate oxygenation (e.g., high FiO_2, high PEEP) • Increased ICP • Hemodynamically unstable
Oral care	Reduce VAP risk by decreasing oropharyngeal colonization	Oral care performed by nursing, including use of chlorhexidine swabs to thoroughly clean inside of mouth	Chlorhexidine gluconate swabs twice daily	No contraindications other than allergy or patient refusal Excessive use may stain teeth May cause mucosal irritation or tongue edema
Stress ulcer prophylaxis	Decrease the risk of SRMD and SRMB (mechanical ventilation >48 hours is an independent risk factor for SRMD and SRMB)	Effective hemodynamic resuscitation Initiation of enteral feeding as soon as possible Pharmacologic therapy	PPIs H_2RAs Sucralfate	PPIs and H2RAs are preferred over sucralfate Conflicting data exist on potential effect of PPIs and H2RAs on VAP because acid-suppression and subsequent rise in gastric pH may allow for bacterial overgrowth and increase in aspiration-related VAP
DVT/PE prophylaxis	Decrease the risk of DVT and PE (critically ill patients are at increased risk of thromboembolic complications)	Nonpharmacologic: • early ambulation • EPC cuffs • IVC filter Pharmacologic	UFH LMWH Fondaparinux	Contraindications/precautions include: • Active bleeding • HIT, history of HIT, hypersensitivity to agent (UFH, LMWHs) • Significant renal impairment (fondaparinux) Monitor: platelets, signs/symptoms of bleeding

DVT = deep venous thrombosis; EPC = external pneumatic compression; FiO_2 = fraction of inspired oxygen; H_2RAs = histamine-2 receptor antagonists; HIT = heparin-induced thrombocytopenia; HOB = head of bed; ICP = intracranial pressure; IVC = inferior vena cava; LMWH = low-molecular-weight heparin; N/A = not applicable. NMBA = neuromuscular blocking agent; PE = pulmonary embolism; PEEP = positive end expiratory pressure; PPIs = proton pump inhibitors; SAT = spontaneous awakening trial; SBT = spontaneous breathing trial; SRMB = stress-related mucosal bleeding; SRMD = stress-related mucosal damage; UFH = unfractionated heparin; VAP = ventilator-associated pneumonia.

Information from: Institute for Healthcare Improvement. Ventilator-Associated Pneumonia [homepage on the Internet].

because of the overuse of antimicrobials; and (3) the potential for adverse drug events. In addition, the oft-cited positive trials of SDD were completed before widespread implementation of the ventilator bundle. Most ventilator bundles include the administration of chlorhexidine gluconate, which is, in effect, a type of SOD. Thus, the incremental benefit of SDD or SOD in today's ICU is unclear. A recent review of this topic details the limitations of available data in ICUs with low and high levels of antimicrobial resistance (Plantinga 2015).

Finally, the role of probiotics for prevention of VAP is limited. Although a relatively small number of studies and reviews have suggested a possible role for probiotics in prevention of VAP, they have not become a part of the routine care of the mechanically ventilated patient (Schultz 2011).

PRINCIPLES OF ANTIMICROBIAL MANAGEMENT OF HAP AND VAP

Several important factors must be considered when using antimicrobials in the management of HAP and VAP. These factors include the use of the local antibiogram for the selection of antimicrobials for empiric therapy, current and emerging patterns of resistance, the pharmacodynamics and pharmacokinetics of antimicrobial agents, and the use of patient-specific culture and susceptibility data in the selection of antimicrobials for definitive therapy. In addition, combination antimicrobial therapy versus monotherapy, time to appropriate antimicrobial therapy, duration of therapy and de-escalation, and dosing and route of administration are all important components of any pharmacotherapeutic plan for HAP and VAP. Finally, general principles for appropriate antimicrobial use to consider include drainage of abscesses, infected fluids, and empyema; removal of infected foreign bodies; and minimizing use of antimicrobials in noninfection (Micek 2006).

Pharmacokinetics and Pharmacodynamics

Significant alterations in the absorption, distribution, metabolism, and excretion of medications are common in the critically ill. Furthermore, the distribution of many antimicrobials into lung tissue and epithelial lining fluid is variable and poor. One approach aimed at improving drug delivery to the infection site in HAP and VAP is the delivery of antimicrobials by inhalation.

Aerosolized antimicrobials can result in increased concentrations at the infection site while limiting systemic toxicity. Although there are no standards of care for this method of delivery, inhalation is often considered in patients who have failed systemic therapy or for multidrug resistant (MDR) pathogens. An example is the use of inhaled tobramycin, which has been used extensively for years in cystic fibrosis patients. Studies and reviews of various inhaled antimicrobials have concluded that outcomes with inhaled therapy are as good as, or better than, outcomes with intravenous therapy (Restrepo 2015). However, many issues related to inhaled therapy continue to be debated, such as appropriate administration technique despite improved inhalation technology, appropriate dose, and whether the inhaled antimicrobial is used as monotherapy or as an adjunctive therapy to intravenous antimicrobials. A recent letter to the editor argued that the inhaled colistin dose in many studies is subtherapeutic for the treatment of MDR gram-negative bacteria (Honore 2015).

Two comprehensive systematic reviews and meta-analyses of aerosolized colistin and aerosolized antimicrobials in the treatment of VAP were recently published. One meta-analysis included eight studies in which aerosolized colistin was administered as an adjunctive therapy to intravenous antimicrobial therapy (colistin or other antimicrobials). The investigators found the addition of aerosolized colistin to improve clinical response over treatment with intravenous therapy alone, although the level of evidence was low (Valachis 2015). The other meta-analysis included 12 studies (6 observational studies, 6 randomized controlled trials) that used a variety of inhaled antimicrobials—colistin, gentamicin, tobramycin, amikacin, ceftazidime, and vancomycin—in addition to intravenous antimicrobials (11 studies) or as monotherapy (1 study). Initial analysis showed a benefit with adjunctive aerosolized therapy (increased clinical cures), but this statistical significance did not carry through in the more rigorous trial sequential analysis. The authors conclude that aerosolized antimicrobials may be useful in the treatment of VAP, but further studies are needed (Zampieri 2015). These two meta-analyses are also good sources for more information on dosing of inhaled antimicrobials.

Exploiting the pharmacodynamic and pharmacokinetic characteristics of various antimicrobials to optimize clinical efficacy and minimize toxicity has also been studied. It is evident that some antimicrobials exhibit concentration-dependent killing and should be administered less often but at a relatively high dose to maximize both the peak/MIC ratio and the drug concentrations in the lung tissue. Examples include aminoglycosides and fluoroquinolones. One of the first publications on this dosing strategy in a large patient population was the use of high-dose, extended-interval aminoglycoside dosing (Nicolau 1995).

Other antimicrobials may exhibit a time-dependent pharmacodynamic profile, and thus the time during the dosage interval that the serum concentration is above the MIC is of importance. These antimicrobials should be administered more often but at a relatively lower dose, possibly as extended infusions or even as continuous infusions. β-Lactams, vancomycin, and some of the carbapenems have been studied using extended-infusion or continuous infusion dosing. A recent multi-center trial demonstrated that extended infusion piperacillin/tazobactam

was associated with decreased mortality compared with standard dosing in critically ill patients with gram-negative infections (Yost 2011).

Although most studies investigating the use of pharmacodynamic-guided dosing are not exclusively performed in HAP or VAP patients, many have included HAP and VAP patients.

Other Principles of Management

Many other issues must be addressed in the patient who has, or is suspected of having, HAP or VAP. Selection of empiric therapy for HAP and VAP is guided by many factors such as suspected pathogens, antibiograms, and individual patient factors (e.g., renal function, comorbidities). Definitive therapy is determined primarily by culture and susceptibility results but also is influenced by patient and external factors. Using combination therapy versus monotherapy for many infections and/or bacterial pathogens, including in HAP and VAP, has been debated and extensively studied. Time to appropriate antimicrobial therapy also has been shown to affect clinical outcomes in infections, including VAP.

Resistance to many of the commonly used antimicrobials for HAP and VAP remains troublesome and has been associated with poorer clinical outcomes and an increased cost of care (Niederman 2001). In one study, risk factors for VAP caused by drug-resistant bacteria included duration of mechanical ventilation, prior antimicrobial use, and prior use of broad-spectrum antimicrobials (Trouillet 1998). Much of the research focus during the early 2000s was on gram-positive organisms (e.g., methicillin-resistant *Staphylococcus aureus* [MRSA]). That focus has shifted to an increasing incidence of resistant gram-negative organisms in HAP and VAP and other nosocomial infections, including *Acinetobacter* spp., *Pseudomonas aeruginosa, Stenotrophomonas maltophilia,* extended-spectrum β-lactamase (ESBL) producing organisms, carbapenem-resistant Enterobacteriaceae, and *Klebsiella pneumoniae* carbapenemase (KPC)-producing bacteria (Table 2-2).

Many strategies have been studied to address resistance across various health care settings, with mixed results. An antimicrobial rotation strategy and its impact on gram-negative pathogens in VAP were evaluated in a single-center, prospective observational study. Investigators found the implementation of an antimicrobial rotation protocol was associated with a decreased incidence of VAP over a 5-year period. In addition, although an initial analysis revealed a nonsignificant increase in the incidence of predefined potentially antimicrobial-resistant gram-negative bacteria, susceptibility patterns of these organisms to the institution's preferred β-lactams either did not significantly change or improved (Gruson 2003).

Finally, de-escalation strategies and therapy duration are important in the management of HAP and VAP. De-escalating therapy and appropriate duration of antimicrobial therapy reduces unnecessary exposure and may decrease the likelihood of adverse events and the induction of antimicrobial resistance.

EMPIRIC ANTIMICROBIAL THERAPY

It is crucial to select an appropriate empiric antimicrobial regimen for the patient with suspected HAP/VAP. It is a well-accepted tenet of practice that prompt initiation of antimicrobials is essential for the patient with a suspected infection. In a classic study, inadequate antimicrobial therapy was found to be a risk factor for mortality in the critically ill (Kollef 1999). Results and analysis of this study suggested the importance of initiating aggressively dosed broad-spectrum antimicrobials. It also furthered interest in the use of combination therapy, especially in empiric treatment, because the use of two or more properly selected antimicrobials is more likely to provide activity against an unknown pathogen than one antimicrobial.

Inappropriate antimicrobial use has also been identified as an independent risk factor for the development of MDR VAP (Royer 2015). Therefore, protocols for the selection of empiric therapy may be beneficial for this therapeutic approach. A prospective before-and-after study assessed the effect of a VAP treatment protocol on the appropriateness of empiric antimicrobial therapy. The incidence of adequate antimicrobial therapy in patients improved from 48% to 94% after implementation of the protocol. Furthermore, there were fewer days of antimicrobial therapy in the protocol group, and the incidence of secondary pneumonia decreased (Ibrahim 2001).

Selection of Antimicrobial Agent(s)

Empiric antimicrobial therapy for VAP should be guided by data whenever possible. Although local and regional susceptibility patterns may be helpful, institution-specific antibiograms should be available and used. Unit-specific antibiograms are even better because resistance patterns often differ across various ICUs within the same institution. As noted previously, initiation of prompt and adequate antimicrobial therapy in critically ill patients is essential, and antibiograms can be useful tools in this effort.

Empiric therapy consists of selecting antimicrobial agents active against likely gram-positive organisms (e.g., MRSA) and gram-negative organisms (e.g., P. *aeruginosa*, other nosocomial pathogens). Guideline-recommended therapies consist of a three-drug combination: (1) vancomycin or linezolid for gram-positive/MRSA coverage; plus (2) an antipseudomonal cephalosporin (cefepime, ceftazidime), or an antipseudomonal carbapenem (imipenem, meropenem), or a β-lactam/β-lactamase inhibitor (piperacillin/tazobactam); plus (3) an antipseudomonal fluoroquinolone (ciprofloxacin, levofloxacin), or an aminoglycoside (gentamicin, tobramycin, amikacin) for gram-negative coverage (ATS/IDSA 2005).

Table 2-2. Resistance in Common HAP/VAP Pathogens and Antimicrobial Treatment Options

Resistance Type	Common HAP/VAP Antimicrobials Affected	Alternatives for HAP/VAP	Comments
Staphylococcus aureus			
Methicillin-resistance (MRSA)	Penicillins Most cephalosporins	Preferred: vancomycin and linezolid Alternatives: teicoplanin, telavancin	Increasing MICs observed with *S. aureus* isolates and vancomycin Increasing incidence of VISA and GISA VRSA and GRSA strains are still rare Tedizolid is being studied for HAP/VAP Tigecycline, daptomycin, and ceftaroline active against MRSA, but not recommended for HAP/VAP
Enterobacteriaceae[a]			
ESBL	Many penicillins, including some with a β-lactamase inhibitor Many cephalosporins Often cross-resistant to other antimicrobial classes	Advanced generation cephalosporins: cefepime, ceftazidime Carbapenems: imipenem/cilastatin, meropenem Fluoroquinolones: ciprofloxacin, levofloxacin Aminoglycosides: gentamicin, tobramycin, amikacin	Ceftolozane/tazobactam is being studied for the treatment of HAP/VAP Resistance may emerge during therapy
Carbapenemase	All carbapenems Often cross-resistant to other antimicrobial classes	Limited options Advanced generation cephalosporins may be active Colistin Ceftolozane/tazobactam often active but no published data on use in VAP Ceftazidime/avibactam may be active against some KPC isolates	Consider using inhaled therapy, alone or added to IV therapy Consider combination therapy May need to use agents reported as resistant in vitro, with possible activity with inhaled and/or combination therapy
Multiple	Almost pan-resistance for some isolates	Limited options Colistin Carbapenems	Consider using inhaled therapy, alone or added to IV therapy Consider combination therapy May need to use agents reported as resistant in vitro, with possible activity with inhaled and/or combination therapy
MDR/XDR *Acinetobacter* spp. *Pseudomonas aeruginosa*			
Multiple mechanisms across multiple classes	Multiple XDR isolates may be resistant in vitro to all available antimicrobials	Limited options Colistin Carbapenems Tigecycline is not active against *Pseudomonas* but may retain activity against some *Acinetobacter* spp. isolates Ampicillin/sulbactam (sulbactam is active component, and may be used without ampicillin if available) Ceftazidime/avibactam may be active against some of these MDR/XDR isolates	Consider using inhaled therapy, alone or added to IV therapy Consider combination therapy May need to use agents reported as resistant in vitro, with possible activity with inhaled and/or combination therapy Ceftolozane/tazobactam not proven to be active against MDR strains of *Acinetobacter*

[a]Enterobacteriaceae includes *Enterobacter, Citrobacter, Serratia, Escherichia coli, Klebsiella*, and *Proteus*.

ESBL = extended-spectrum β-lactamase; GISA = glycopeptide-intermediate *Staphylococcus aureus*; GRSA = glycopeptide-resistant *S. aureus*; HAP = hospital-acquired pneumonia; IV = intravenous; KPC = *Klebsiella pneumoniae* carbapenemase; MDR = multidrug-resistant; MIC = minimum inhibitory concentration; MRSA = methicillin-resistant *S. aureus*; VAP = ventilator-associated pneumonia; VISA = vancomycin-intermediate *S. aureus*; VRSA = vancomycin-resistant *S. aureus*; XDR = extensively drug-resistant.

Patient Care Scenario

K.G. is a 52-year-old man who is admitted to the trauma ICU after surgery to repair an open fracture of the left tibia and fibula suffered in a motorcycle crash. He also has left-sided fractures of ribs 4-8, left-sided pulmonary contusions and hemothorax, and a left thoracostomy tube. K.G. has a reported allergy to penicillin (rash and itching). His medical history includes type 1 diabetes, hypertension, coronary artery disease, hyperlipidemia, and stage II chronic kidney disease. He received intravenous clindamycin and gentamicin for 48 hours after surgery. K.G. has remained intubated, sedated, and on mechanical ventilation since admission. On hospital day 5, he now has a left upper lobe infiltrate on chest radiography, his WBC has increased from 7.1 x 10^3 cells/mm^3 to 16.4 x 10^3 cells/mm^3, and his T_{max} over the past 24 hours is 39.2° C. What antimicrobial therapy, if any, should be started for K.G.?

ANSWER

This patient is at a high risk of HAP and VAP. He has been intubated and in an ICU for 5 days; he has multiple rib fractures, a hemothorax, and a thoracostomy; and he recently finished a 3-day course of broad-spectrum antimicrobials. He now has signs and symptoms consistent with HAP and VAP. After having been in the hospital and on a ventilator for 5 days, he is febrile, has a leukocytosis, and has a new infiltrate on chest radiography. Guidelines recommend starting aggressively dosed broad-spectrum combination therapy in this patient. Antimicrobial therapy should include vancomycin or linezolid to cover for MRSA, plus either an antipseudomonal cephalosporin, carbapenem, or β-lactam/β-lactamase inhibitor, plus either an antipseudomonal fluoroquinolone or aminoglycoside to cover a broad array of gram-negative organisms including *P aeruginosa*. One possible regimen might be vancomycin plus meropenem plus ciprofloxacin. In this regimen, vancomycin was simply chosen as one of two options considered equivalent, meropenem was chosen to avoid a possible allergic reaction to a β-lactam agent, and ciprofloxacin was chosen to avoid longer-term aminoglycoside therapy in a patient with a history of chronic kidney disease. The practitioner needs to use the local antibiogram to guide specific selections. Dosing should be aggressive, but must take into account this patient's renal function.

1. American Thoracic Society; Infectious Diseases Society of America: guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am J Respir Crit Care Med 171;2005:388-416.
2. Wunderink RG, Niederman MS, Kollef MH, et al. Linezolid in methicillin-resistant *Staphylococcus aureus* nosocomial pneumonia: a randomized, controlled study. Clin Infect Dis 2012;54:621-9.
3. Kollef MH, Sherman G, Ward S, et al. Inadequate antimicrobial treatment of infections: a risk factor for hospital mortality among critically ill patients. Chest 1999;115:462-74.

Unless a patient is significantly immunocompromised or has other extenuating circumstances, neither antifungal nor antiviral therapy are indicated as empiric therapy for VAP (Table 2-3).

Combination Therapy vs. Monotherapy

Debate continues on combination therapy versus monotherapy for the definitive treatment of some of the nosocomial gram-negative organisms. However, because of continued resistance in many common gram-negative pathogens implicated in VAP, combination therapy for the empiric treatment of VAP is widely accepted. Using combination therapy with appropriately chosen drugs increases the likelihood that the initial regimen will adequately cover the causative organism. The specific agents chosen should depend on the institutional antibiogram and patient-specific factors (e.g., preference for a fluoroquinolone vs. an aminoglycoside in a patient at high risk of acute kidney injury).

For the empiric coverage of the gram-positive organisms likely to cause VAP (primarily MRSA), monotherapy is recommended, typically with vancomycin or linezolid. Other anti-MRSA antimicrobials (e.g., ceftaroline, daptomycin, tedizolid, telavancin, tigecycline) cannot be routinely recommended as first-line empiric therapy because of clinical inferiority or lack of data, as discussed in the following.

Of note is the distinction between combination therapy for the empiric treatment of VAP (recommended), and combination therapy for definitive therapy (not routinely recommended). Although combination therapy for the definitive treatment of *P. aeruginosa* and occasionally other nosocomial gram-negatives (e.g., *Acinetobacter baumannii*) is commonly advocated, little or no evidence exists to support this recommendation in pneumonia. Although one study did show a decreased mortality in patients with documented *P. aeruginosa* bacteremia who received combination therapy compared to those who received monotherapy, these results cannot be directly extrapolated to pneumonia patients (Chamot 2003).

Therapy Duration and De-escalation Strategies

Once empiric therapy has been initiated, the decision must subsequently be made to either continue the current antimicrobial regimen, adjust the current antimicrobial regimen, or to simply discontinue all antimicrobials. This decision is not only based on culture and susceptibility data but also on clinical factors (e.g., WBC, temperature, chest radiography).

Table 2-3. Empiric Therapy for HAP/VAP

Suspected Pathogen(s)	Recommended Antimicrobial(s)
Gram-positive bacteria, including MRSA	Linezolid or vancomycin PLUS
Gram-negative bacteria, including common MDR pathogens: • Enterobacteriaceae[a] • *Pseudomonas aeruginosa* • *Acinetobacter* spp.	Antipseudomonal cephalosporin (cefepime or ceftazidime) OR Antipseudomonal carbapenem (imipenem or meropenem) OR Antipseudomonal β-lactam/β-lactamase inhibitor (piperacillin/tazobactam) PLUS Antipseudomonal fluoroquinolone (ciprofloxacin or levofloxacin) OR Aminoglycoside (gentamicin, tobramycin, or amikacin)

[a]Enterobacteriaceae includes *Enterobacter, Citrobacter, Serratia, Escherichia coli, Klebsiella,* and *Proteus*.

HAP = hospital-acquired pneumonia; MDR = multidrug-resistant; MRSA = methicillin-resistant *S. aureus*; VAP = ventilator-associated pneumonia.

Information from: American Thoracic Society; Infectious Diseases Society of America: guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am J Respir Crit Care Med 2005;171:388-416.

The Clinical Pulmonary Infection Score (CPIS) has been studied for its potential to identify patients in whom empiric VAP therapy can be safely discontinued. The CPIS uses an assessment of a patient's temperature, WBC, secretions, oxygenation, chest radiography, and sputum culture data to assign a point value (Table 2-4). A score of 6 or less indicates it is not likely that the patient has pneumonia, whereas a score greater than 6 indicates likely pneumonia. In one study evaluating the utility of the CPIS, 81 patients with an initial CPIS of 6 or less being empirically treated for VAP were assigned to

Table 2-4. Clinical Pulmonary Infection Score

Clinical Factor	Pulmonary Infection Score Points		
	0	1	2
Temperature (C°)	36.5–38.4	38.5–38.9	≥39.0 or ≤36.0
Leukocyte count (mm^3)	≥4000 to <11,000	<4000 or >11,000	<4000 or >11,000 and ≥50% immature band forms
Tracheal secretions	None	Nonpurulent	Purulent
Oxygenation (PaO_2/FiO_2 ratio)	>240 or ARDS	—	≤240 and no ARDS
Chest radiography	No infiltrates	Diffuse infiltrates	Localized infiltrates
Progression of infiltrate	No progression	—	Progression (after CHF and ARDS excluded)
Culture of tracheal aspirate	Rare or light quantity or no growth	Moderate or heavy growth pathogenic bacteria	Same pathogenic bacteria seen on Gram stain

ARDS = acute respiratory distress syndrome; CHF = congestive heart failure; PaO_2/FiO_2 ratio = ratio of arterial oxygen pressure to fraction of inspired oxygen.

Information from: Singh N, Rogers P, Atwood CW, et al. Short-course empiric antibiotic therapy for patients with pulmonary infiltrates in the intensive care unit. A proposed solution for indiscriminate antibiotic prescription. Am J Respir Crit Care Med 2000;162:505-11.

one of two groups: treatment protocol using the CPIS (n=39) or standard therapy per physician discretion (n=42). Patients were reassessed on day 3 after antimicrobial initiation. Antimicrobial therapy was discontinued for patients with a CPIS of 6 or less, and therapy was continued (and modified, if necessary) for patients with a CPIS greater than 6, based on culture and susceptibility results and according to physician discretion for the remainder of the study. Patients in the CPIS group had a shorter duration of antimicrobial therapy and ICU length of stay and lower 30-day mortality and antimicrobial costs than did patients in the standard therapy group (Singh 2000). Although these results are intriguing, they have not been confirmed in subsequent studies, and the routine use of a calculated CPIS for discontinuing antimicrobial therapy cannot be recommended.

With respect to duration of antimicrobial therapy, an 8-day antimicrobial regimen was compared with a 15-day regimen in patients with clinically proven gram-negative VAP (Chastre 2003). Patients in the 8-day group had similar outcomes (mortality, recurrence, relapse, and superinfections) but significantly more antimicrobial-free days than did the 15-day group. One caveat in this study is that patients with VAP caused by non–lactose-fermenting gram-negative bacilli (e.g., *P. aeruginosa*) treated for 8 days had a higher rate of recurrent infections than did those for treated 15 days.

A randomized controlled trial compared a discontinuation policy for suspected VAP with standard practice, evaluating the primary outcome of duration of antimicrobial therapy and secondary outcomes including mortality, length of hospital and ICU stay, days of mechanical ventilation, and VAP recurrence (Micek 2004). Patients in the formal discontinuation protocol group received significantly fewer days of antimicrobials than did the standard practice group (6 vs. 8 days, p=0.001). Secondary outcomes were similar in the two groups. The authors concluded that the use of a protocol can be a safe and effective approach in guiding the discontinuance of antimicrobial therapy in clinically suspected VAP.

Not all de-escalation studies have shown uniformly positive results across outcome measures. A randomized controlled trial compared an empiric regimen of vancomycin plus imipenem/cilastatin with de-escalation to a regimen of conventional antimicrobials (no vancomycin, no carbapenems) without de-escalation (Kim 2012). There was an increase in the emergence of MDR organisms (particularly *S. aureus*) in the de-escalation group within 1 month of therapy. However, mortality and length of stay were similar between the two groups.

Although invasive procedures (e.g., bronchoscopy, bronchoalveolar lavage, protected specimen brush samples) are most often used and studied as diagnostic interventions, the effect of these techniques on the duration and overall use of antimicrobials has also been evaluated. A study comparing invasive (bronchoscopy with protected brush specimen samples, bronchoalveolar lavage) and noninvasive strategies (sputum Gram stain and culture) in the management of suspected VAP demonstrated more antimicrobial-free days, fewer antimicrobials per day, decreased colonization of infection with *Candida* spp., quicker improvement in organ dysfunction scores, and a lower 14-day mortality rate in the invasive strategy group (Fagon 2000). Invasive strategies may also improve the selection of antimicrobial therapy, given their improved yield. On further analysis, the investigators found that patients in the noninvasive group were more likely to have at least one pathogen resistant to the initially prescribed antimicrobial. The mortality rate in these patients (32.0%) was higher than in patients who received adequate therapy (20.4%), although this difference was not statistically significant.

The adjustment of empiric antimicrobial therapy is as important as the appropriate duration of therapy. Typically, adjustments are made according to culture and susceptibility results once they are available. This strategy is generally referred to as *de-escalation* because the most common adjustment is discontinuing one or more of the empiric antimicrobials and/or changing the broad-spectrum agents to narrower spectrum antimicrobials that are active against the identified pathogen(s). De-escalation strategies are an effective way to decrease antimicrobial resistance and may also decrease adverse drug events and cost. In an observational study of 1596 critically ill surgical patients, of whom 138 had a diagnosis of VAP, investigators found no statistically significant differences in mortality or recurrent pneumonia between patients who had de-escalated antimicrobial therapy versus patients who did not (Eachempati 2009). It must be noted that although the idea of de-escalation is relatively straightforward, it is not always easily implemented. In one study, the empiric antimicrobial regimen was excessive and de-escalation was possible in 95% of the studied population; however, de-escalation only occurred in 62% of these patients (Prinapori 2013).

Investigators continue to pursue innovative ways to distinguish between infectious and noninfectious pathologies and to identify pathogens earlier in hope of decreasing unnecessary antimicrobial use. These techniques include the use of a procalcitonin assay, peptide nucleic acid fluorescent in situ hybridization, and polymerase chain reaction testing (Layios 2013; Arnold 2011).

DEFINITIVE ANTIMICROBIAL THERAPY

As previously noted, it is important to adjust the empiric antimicrobial regimen once the causative pathogen is known. For this discussion, however, is not possible to discuss all antimicrobial regimens for all of the possible VAP pathogens. Similarly, a comprehensive discussion of antimicrobial resistance and related topics (e.g., incidence, epidemiology, mechanisms, attributable morbidity, mortality and cost, risk

factors) is beyond the scope of this chapter. Antimicrobial resistance is fully covered in another chapter. The following sections discuss antimicrobial options for the treatment of VAP caused by common MDR pathogens.

MRSA and Other Gram-Positive Organisms

For HAP overall, 50%–60% of cases are caused by MRSA (Jones 2010). Vancomycin, a glycopeptide antimicrobial, remains the mainstay for the treatment of HAP/VAP caused by MRSA in most institutions. Although the phenomenon referred to as *MIC creep* (i.e., increasing MICs for vancomycin against MRSA over time) has been observed, fully resistant strains remain rare.

Concerns with vancomycin have led to interest in alternative therapies for MRSA VAP. These concerns include (1) difficulty in dosing and need for pharmacokinetic monitoring; (2) poor penetration into lung tissue; (3) the potential, albeit low risk, of nephrotoxicity, especially when combined with other commonly used antimicrobials such as aminoglycosides and piperacillin/tazobactam; and (4) infusion-related reactions. Although guidelines recommend higher vancomycin serum trough concentrations (greater than 15 mg/L), this recommendation was mainly based on pharmacokinetic and pharmacodynamic models. A more recent publication has suggested that there is no additional clinical benefit to higher troughs but an increased incidence of nephrotoxicity (Lodise 2009). A recent post hoc analysis showed no difference in clinical outcomes but a trend toward higher mortality and a higher incidence of nephrotoxicity associated with higher vancomycin serum trough concentrations (Barriere 2014).

Linezolid, an oxazolidinone, is typically the most common alternative to vancomycin and has FDA-approved labeling for the treatment of nosocomial pneumonia (among other infections) caused by MRSA. Linezolid does not require dosing adjustments for renal dysfunction or serum monitoring and extensively penetrates into lung tissue.

Two large, randomized controlled trials showed linezolid to be noninferior to vancomycin in the treatment HAP and HCAP caused by MRSA (Wunderink 2003; Rubinstein 2001). Subsequent post hoc analyses of these trials suggested that linezolid may be superior to vancomycin for the treatment of MRSA pneumonia (Kollef 2004; Wunderink 2003). However, further investigations have refuted this assertion, including a meta-analysis comparing linezolid with two glycopeptides: vancomycin and teicoplanin (Kalil 2010). A more recent randomized controlled study comparing linezolid with dose-optimized vancomycin showed better clinical response in linezolid-treated patients but no difference in mortality between groups (Wunderink 2012).

Linezolid use is contraindicated with monoamine oxidase inhibitors, and it must be used with caution with serotonergic agents (e.g., selective serotonin reuptake inhibitors), with dopaminergic and sympathomimetic agents, and in patients with liver injury. Linezolid can cause myelosuppression (usually with use beyond 7–14 days) that most commonly manifests as thrombocytopenia, and the acquisition cost is significantly greater than that of vancomycin. An advantage is that linezolid is one of the only oral options available for MDR gram-positive organisms, although enteral absorption in the critically ill may not be optimal.

Teicoplanin is a glycopeptide active against MRSA and other gram-positive bacteria; it is approved outside the United States for the treatment of many infections caused by gram-positive organisms, but not nosocomial pneumonia. Teicoplanin is recommended by the British Thoracic Society as an alternative to vancomycin and linezolid for the treatment of community-acquired MRSA pneumonia (Lim 2009). Two randomized controlled trials compared teicoplanin with linezolid for the treatment of infections caused by gram-positive organisms (Cepeda 2004; Wilcox 2004). Both studies included patients with pneumonia: the first study enrolled a mix of patients with community-acquired pneumonia and HAP, whereas the second study enrolled only critically ill patients with nosocomial pneumonia, most of whom were receiving mechanical ventilation. The first study found linezolid superior to teicoplanin for clinical cure rates in all patients and infections combined. However, there was no difference between groups in the patients treated for pneumonia. In the second study, clinical and microbiologic success, mortality, and adverse events were similar between the teicoplanin and linezolid groups. A meta-analysis comparing linezolid with vancomycin and teicoplanin showed noninferiority between agents for clinical cure and microbiologic eradication rates, but a higher incidence of thrombocytopenia and gastrointestinal events was seen with linezolid (Kalil 2010).

Telavancin is a lipoglycopeptide indicated for the treatment of nosocomial pneumonia (including VAP) caused by either methicillin-susceptible *Staphylococcus aureus* or MRSA. In two methodologically identical studies published as a single article (the ATTAIN trials), telavancin was compared with vancomycin for the treatment of gram-positive HAP. Both studies met the primary end point of noninferiority for clinical response in both the all-treated and clinically evaluable populations. Adverse events were similar across all groups, although increases in SCr were higher in patients receiving telavancin (16 vs. 10%, no p value) (Rubinstein 2011).

Because of new FDA standards for the diagnosis and end points in nosocomial pneumonia trials, the same investigators performed a post hoc analysis of the ATTAIN trials (Corey 2014). Using the new diagnostic criteria and a 28-day mortality rate end point, the investigators again found telavancin noninferior to vancomycin. However, 28-day survival was lower in the telavancin group in patients with pre-existing moderate-to-severe renal impairment, defined as an estimated CrCl less than 50 mL/minute. Other post hoc subgroup analyses of the ATTAIN studies using various patient and clinical factors (e.g., presence of renal impairment, vancomycin serum trough concentrations, presence of bacteremia,

whether patients were intubated and receiving mechanical ventilation) produced results similar to the entire ATTAIN trial population.

Tedizolid is a newer-generation oxazolidinone with activity against MRSA; it is approved for the treatment of acute skin and skin structure infections. Because of its potency and pharmacokinetic profile, tedizolid is dosed once daily versus the twice-daily dosing for linezolid. Early clinical experience indicates that tedizolid may have fewer drug interactions than linezolid and a more favorable safety profile, particularly a lower incidence of thrombocytopenia (Rybak 2015). Tedizolid is currently being studied for use in nosocomial pneumonia.

Many other agents are active against MRSA but are either not indicated for nosocomial pneumonia or have not been adequately studied. Daptomycin is an option for the treatment of bloodstream, skin, and other infections caused by MSSA and MRSA. However, it is contraindicated for the treatment of pneumonia because it is inactivated by pulmonary surfactant (Silverman 2005). Ceftaroline, an advanced-generation cephalosporin with MRSA activity, is indicated for the treatment of community-acquired pneumonia but not HAP or VAP. Limited observational data describing its off-label use suggest a possible role in the definitive treatment of VAP caused by pathogens susceptible to ceftaroline (Kaye 2015).

Gram-Negative Organisms

Many antimicrobials in clinical use years ago are still commonly used for nosocomial gram-negative organisms; these include the extended-spectrum penicillins (e.g., piperacillin/tazobactam), extended-spectrum cephalosporins (e.g., ceftazidime, cefepime), carbapenems (e.g., imipenem/cilastatin, meropenem), aminoglycosides, and aztreonam. Definitive therapy, as discussed previously, is guided not only by susceptibility results but also by individual patient and drug factors. In the following discussion of these circumstances, the focus is on MDR pathogens and the newer agents and novel therapies.

Extended-Spectrum β-Lactamase (ESBL) and Carbapenemase-Producing Organisms

A particularly problematic group of highly resistant gram-negative bacteria often implicated in HAP and VAP are the ESBL-producing organisms. These bacteria are often described by the acronyms SPICE or SPACE (Box 2-1). Some of these organisms may also produce KPC enzymes, thereby conferring resistance to the carbapenems. *Klebsiella pneumoniae* is notorious for being both an ESBL and KPC producer, whereas *Escherichia coli* is commonly an ESBL producer.

Select β-lactams and carbapenems retain activity against ESBL- and carbapenemase-producing bacteria. Cefepime, a fourth-generation cephalosporin, and piperacillin/tazobactam may be used, but resistance is increasing. Although resistance to imipenem/cilastatin and meropenem is emerging, carbapenems are still considered the drugs of choice for treatment of ESBL-producing bacteria. The cephalosporin/β-lactamase inhibitor combination antimicrobials ceftolozane/tazobactam and ceftazidime/avibactam were recently approved in the United States for the treatment of complicated urinary tract infections, pyelonephritis, and complicated intra-abdominal infections.

Ceftolozane is structurally similar to ceftazidime, but modification of the cephem nucleus side-chain and addition of the tazobactam component results in activity against some MDR bacteria, as well as some anaerobes (Melchers 2015; Farrell 2014; Zhanel 2014). In a study evaluating the susceptibility of gram-negative isolates from patients with pneumonia, ceftolozane/tazobactam showed excellent in vitro activity against many MDR *P. aeruginosa* isolates and ESBL-producing *E. coli* and *K. pneumoniae*. However, ceftolozane/tazobactam and other β-lactams in the study had poor activity against *Acinetobacter* spp. and *Stenotrophomonas maltophilia*, a reminder of the inherent difficulty in treating these MDR isolates (Farrell 2014). Ceftolozane/tazobactam is not active against bacteria that produce serine carbapenemases and metallo-β-lactamases. Although ceftolozane/tazobactam has no indication for the treatment of pneumonia, a large phase III trial comparing ceftolozane/tazobactam with meropenem in the treatment of HAP and VAP is currently under way. Both pharmacokinetic and pharmacodynamic studies have shown adequate penetration into lung tissue and epithelial lining fluid after systemic dosing (Xiao 2015; Chandorkar 2012).

Ceftazidime has been approved and used for many years; avibactam is a newer, more potent, and broader-spectrum β-lactamase inhibitor with a different mechanism of action from currently used β-lactamase inhibitors. In a study evaluating the susceptibility of gram-negative isolates from ICU and non-ICU patients including those with VAP, ceftazidime/avibactam showed excellent in vitro activity against *P. aeruginosa* and MDR and extensively drug resistant strains of Enterobacteriaceae

Box 2-1. Acronyms Describing ESBL-producing Organisms

SPICE
- *Serratia* spp.
- *P. aeruginosa*
- Indole-positive Proteeae (*Proteus vulgaris, Morganella morganii, Providencia* spp.)
- *Citrobacter* spp.
- *Enterobacter cloacae*

SPACE
- *Serratia* spp.
- *P. aeruginosa*
- *Acinetobacter* spp.
- *Citrobacter* spp.
- *Enterobacter cloacae*

ESBL = extended-spectrum β-lactamase.

(Sader 2015). Ceftazidime/avibactam has not been evaluated in the treatment of pneumonia, but its activity against KPC may prove important as resistance continues to emerge in HAP and VAP pathogens. However, ceftazidime/avibactam resistance in a KPC-producing *K. pneumoniae* isolate has already been reported (Humphries 2015).

Tigecycline, a broad-spectrum glycylcycline and derivative of minocycline, is approved for use in complicated intra-abdominal infections, complicated skin and skin structure infections, and community-acquired pneumonia in the United States. It is active against many gram-positive and gram-negative organisms, including MRSA. In a study comparing tigecycline plus ceftazidime to imipenem/cilastatin plus vancomycin for HAP, tigecycline was noninferior to the imipenem/cilastatin group in overall cure rates in the modified intent-to-treat population. However, tigecycline did not meet the noninferiority endpoint in the clinically evaluable population. In addition, in the VAP group, more deaths occurred in the tigecycline group (p=0.168). Finally, for patients in whom MRSA was the causative organism, cure rates were lower in both the VAP and non-VAP groups (Freire 2010). Subsequent meta-analyses including this study and other phase III and phase IV studies (patients treated with tigecycline for both approved and off-label use) prompted the FDA to issue a boxed warning for an observed increase in all-cause mortality. Therefore, tigecycline cannot be recommended as a routine alternative for the treatment of VAP, although exceptions may exist, as discussed in the section on VAP caused by *Acinetobacter* spp.

Although fluoroquinolones are still considered broad-spectrum gram-negative antimicrobials, the MDR pathogens are often resistant, and the fluoroquinolones should only be used when susceptibility results dictate. If the organism is susceptible, then fluoroquinolones may be a good option because they exhibit good lung penetration, have a relatively good safety profile, and may be an alternative to aminoglycosides when nephrotoxicity is of concern. They are often used in combination with cell-wall active agents such as β-lactams, although the benefit of such combinations in the definitive treatment of nosocomial pneumonia is unclear. Ciprofloxacin and levofloxacin are the most commonly used intravenous fluoroquinolones for HAP/VAP.

With the advent of newer agents active against *Pseudomonas* and other nosocomial gram-negative pathogens, the aminoglycosides are used less often. Of particular concern is the potential for ototoxicity and nephrotoxicity. Also, aminoglycosides should not be used as monotherapy for nosocomial pneumonia, only in combination with cell-wall active agents (e.g., penicillins, cephalosporins). Nonetheless, aminoglycosides still play a role in the treatment of HAP and VAP because of an increasing incidence of MDR gram-negative organisms. Gentamicin, tobramycin, and amikacin are the aminoglycosides used for systemic therapy in the United States. There is a great deal of interest in the use of inhaled antimicrobials, including the aminoglycosides, for the treatment of HAP and VAP, as previously discussed.

Acinetobacter baumannii

An especially problematic VAP pathogen *is A. baumannii*; it is commonly MDR and has recently been described as extensively drug resistant (i.e., exhibits resistance through multiple mechanisms) (Qureshi 2015; Agodi 2014). Attributable mortality associated with *A. baumannii* VAP has been reported to be 70%–80% (Viehman 2014). Independent risk factors for acquiring *A. baumannii* VAP include trauma on hospital admission and inappropriate antimicrobial therapy (Royer 2015). In another study, independent risk factors for mortality in patients with *A. baumannii* VAP were chronic obstructive pulmonary disease, diabetes mellitus, and lack of clinical response to the prescribed therapy (Yilmaz 2015). Guidance on antimicrobial therapy for *A. baumannii* VAP remains a challenge: much of the published literature is based on in vitro or animal model studies and on humans with retrospective and/or observational studies with no comparator or control and small numbers of patients.

Imipenem and meropenem are active against some *Acinetobacter* isolates, but resistance is already high and continues to increase. In a cohort of ICU patients admitted for VAP, 59% of the *A. baumannii* isolates were resistant to imipenem. Of those resistant strains, 71% tested positive for class D carbapenemase production (Royer 2015).

Ampicillin/sulbactam may be used alone if the organism is susceptible, but it is often added to other antimicrobials such as carbapenems or colistin. Sulbactam alone can be added because it is the sulbactam component that is active against some strains of *A. baumannii*; however, sulbactam alone is not available in the United States. In a study comparing ampicillin/sulbactam with colistin for the treatment of *A. baumannii* nosocomial pneumonia, outcomes were similar between groups (Betrosian 2008). Results of this trial are discussed in the colistin section.

Typically, *A. baumannii* is susceptible to tigecycline. However, inducible efflux pump overexpression may occur, with subsequent emergence of resistance. Clinical data on the use of tigecycline for *Acinetobacter* spp. VAP is limited to observational studies or in the examination of data subsets in previous studies. In a phase III study evaluating VAP, the clinical response rates for patients infected with *A. baumannii* receiving tigecycline or imipenem were 57% and 95%, respectively (Freire 2010). As mentioned previously, it is important to note that the package insert for tigecycline contains a boxed warning for an observed increase in all-cause mortality in tigecycline-treated patients versus comparators. Nonetheless, tigecycline may be considered as an option in the treatment of MDR *A. baumannii* VAP, usually in combination with other antimicrobials.

Colistin (polymyxin E or colistimethate sodium) is one of two polymyxin agents approved for use in the United States.

Because of concerns with nephrotoxicity, difficulty in dosing, and poor penetration into lung tissue, colistin historically was scarcely used. However, with the increasing incidence of MDR and extensively drug resistant *A. baumannii* and other MDR gram-negatives, colistin now is commonly used in some ICUs and has become a first-line therapy for MDR/extensively drug resistant *A. baumannii* VAP. Many *A. baumannii* strains are resistant to all drugs except colistin. In a recent U.S. study, almost 95% percent of *A. baumannii* isolates were susceptible to colistin (Quennan 2012). However, reports of colistin-resistant strains are becoming more common, including emergence during colistin therapy because of selection of a resistant subpopulation (Li 2006).

In the only prospective, controlled trial to date comparing colistin with an alternative therapy, 30 patients with *A. baumannii* VAP were randomized to either intravenous colistin or intravenous ampicillin/sulbactam (Betrosian 2008). In the 28 patients evaluated, clinical response (defined as a resolution of the signs and symptoms of VAP) was achieved in 60% and 61.5% of the colistin and ampicillin/sulbactam patients, respectively. Microbiologic eradication and mortality were similar between the two groups. Adverse events were not statistically different, but this finding was likely because of a very small sample size. Nephrotoxicity (defined as a prespecified percentage increase in the SCr depending on the patient's baseline value) occurred in 33.3% of the patients taking colistin and in 15% of patients taking ampicillin/sulbactam. Therapy was not discontinued prematurely because of an adverse event in either group.

Combination therapy for the definitive treatment of VAP has no proven benefit in gram-negative pneumonia. However, several factors have led to the use of combination therapy in VAP caused by *A. baumannii*, each with varying levels of success, including (1) extensive resistance patterns, (2) high mortality associated with *A. baumannii* VAP, (3) unpredictable and suboptimal pharmacokinetics of colistin and tigecycline, (4) emergence of resistance during colistin and tigecycline monotherapy, and (5) uncertainty with sulbactam dosing and translation of in vitro efficacy to clinical success. Multiple combinations of antimicrobials have been evaluated (including some in which one or both antimicrobials have no activity for the particular strain of *Acinetobacter*) in the hope of an additive or synergistic effect. Most combinations include colistin as one of the agents; other components include aminoglycosides, antipseudomonal β-lactams and fluoroquinolones, carbapenems, intravenous fosfomycin (not available in the United States), glycopeptides, rifamycins, sulbactam, tigecycline, and trimethoprim/sulfamethoxazole. These all have produced limited success (Viehman 2014; Falagas 2005).

Aerosolized antimicrobials (e.g., with colistin) are often used as adjunctive therapy in the treatment of VAP caused by *A. baumannii*, *P. aeruginosa*, and other MDR gram-negative bacteria. Aerosolized therapy is discussed earlier in this chapter.

Patient Care Scenario

K.G., the 52-year-old man featured in the earlier Patient Care Scenario, has been started on empiric antimicrobials and is responding well to therapy. His WBC is now normal, he is afebrile, and the infiltrate on chest radiography is improving. K.G.'s sputum cultures are positive for *Klebsiella pneumoniae*. This isolate is ESBL- and carbapenemase-negative. It is fully susceptible to multiple advanced generation cephalosporins, fluoroquinolones, carbapenems, aminoglycosides, and β-lactam/β-lactamase inhibitors. What is best to recommend now as antimicrobial therapy for K.G.?

ANSWER

This patient's antimicrobials should be de-escalated to a single agent active against the cultured isolate of *K. pneumoniae*. Ideally, the choice should also be as narrow-spectrum as possible. Actual selection of the specific antimicrobial should be guided by the culture and susceptibilities, keeping in mind the patient's reported penicillin allergy. Antimicrobials should be continued for a total of 8 days.

1. American Thoracic Society; Infectious Diseases Society of America: guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am J Respir Crit Care Med 171;2005:388-416.

2. Chastre J, Wolff M, Fagon JY, et al. Comparison of 8 vs 15 days of antibiotic therapy for ventilator-associated pneumonia in adults: a randomized trial. JAMA 2003;290:2588-98.

CONCLUSION

Despite increased awareness, better methods for prevention, and the recent introduction of new antimicrobial therapies, HAP and VAP remain a problem in the management of the critically ill patient, with significant attributable morbidity and mortality. Evidence-based U.S. and international guidelines guide the practitioner in preventing and treating HAP and VAP; however, many more studies have been published since these guidelines were released. The pharmacist can play an important role in the prevention of HAP and VAP and their associated complications (e.g., by helping to implement a ventilator bundle), as well as in the treatment of HAP and VAP. Important aspects of care for the pharmacist on the interprofessional team include selection of empiric and definitive antimicrobials and use of pharmacokinetics and pharmacodynamics to optimize therapy.

Empiric therapy for HAP and VAP should include a combination of (1) an agent against MRSA (vancomycin or linezolid), and (2) two antipseudomonal agents, either a β-lactam or carbapenem, plus a fluoroquinolone or an aminoglycoside. Definitive therapy and/or de-escalation should be guided by patient factors, clinical response, and microbiologic results. Dosing should be aggressive because inadequate antimicrobial therapy (selection and dose) is a predictor of increased mortality. Appropriate dosing may be especially challenging in the critically ill patient because many ICU patients

are obese, have changing renal function (and may be receiving renal replacement therapy), exhibit changes in volume of distribution, and have other pharmacokinetic and pharmacodynamic alterations. The pharmacist may also need to consider the need for aerosolized antimicrobial therapy. Goals of therapy should be defined and monitored, such as clinical response and microbiologic eradication, and monitoring for treatment-related adverse events should occur as well.

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Practice Points

The pharmacist can play an important role in the management of HAP/VAP in the ICU as part of an interprofessional team. Although comprehensive, evidence-based guidelines are available, they are now more than 10 years old. Many of the same principles apply today; however, newer antimicrobials have been introduced. The epidemiology of the causative pathogens continues to change, resulting in continuing problems with resistance, despite the advent of new antimicrobials.

- **Prevention: HAP/VAP prevention is important. The pharmacist can help implement a ventilator bundle. Elevation of the head of the bed, daily spontaneous breathing trials, and daily oral care with chlorhexidine can reduce the incidence of VAP. Stress ulcer prophylaxis and deep venous thrombosis prophylaxis can help reduce complications associated with mechanical ventilation.**
- **Route of administration: Intravenous antimicrobials are still the mainstay of antimicrobial therapy for HAP/VAP. However, aerosolized antimicrobials are becoming more important with the increasing incidence of MDR isolates and clinical failures.**
- **Empiric therapy: Empiric antimicrobial therapy for HAP/VAP should be initiated promptly with aggressive dosing of broad-spectrum agents. Therapy should include an agent with good gram-positive activity against MRSA plus two agents with good gram-negative activity against *P. aeruginosa.***
- **Definitive therapy / De-escalation: Empiric therapy should be adjusted as soon as patient response and culture results dictate. Typically this means a de-escalation of therapy to a single agent, often with a narrower spectrum of activity. However, antimicrobials may need to be adjusted earlier if the patient is not responding to therapy.**
- **Duration / Discontinuation: In patients initially with suspected pneumonia, antimicrobials can be discontinued as early as 5 days after initiation of therapy, if the patient is stable and is low risk (e.g., a low CPIS score). Patients with confirmed VAP who receive 8 days of antimicrobials have similar outcomes as those receiving 15 days, with exception of possibly a higher incidence of recurrent infections in VAP cases caused by non–lactose-fermenting gram-negative organisms (i.e., *P. aeruginosa*).**
- **Antimicrobials for gram-positive pneumonia: Vancomycin and linezolid remain the first-line agents for MRSA pneumonia. Teicoplanin (not available in the United States) and telavancin are alternatives in most cases. Tigecycline, daptomycin, and ceftaroline cannot be recommended at this time. Tedizolid is being studied for nosocomial HAP/VAP.**
- **Antimicrobials for gram-negative pneumonia: Antipseudomonal penicillins, advanced generation cephalosporins, carbapenems, fluoroquinolones, and aminoglycosides still form the backbone of therapy for gram-negative HAP/VAP. However, an increasing incidence of MDR/extensively drug-resistant organisms, in particular *P. aeruginosa* and *A. baumannii*, has necessitated the (re)evaluation of both old and new drugs, such as colistin, sulbactam, tigecycline, ceftolozane/tazobactam, and ceftazidime/avibactam.**

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Zhanel GG, Chung P, Adam H, et al. Ceftolozane/tazobactam: a novel cephalosporin/β-lactamase inhibitor combination with activity against MDR gram-negative bacteria. Drugs 2014;74:31-51.

Self-Assessment Questions

Questions 21–23 pertain to the following case.

A.B. is a 72-year-old man admitted to the surgical ICU after open repair of an aortic abdominal aneurysm. He arrives to the ICU intubated and mechanically ventilated. On Day 6 of hospitalization, A.B. has a new left upper lobe infiltrate on chest radiography, his WBC has increased from 8.2 x 10^3 cells/mm^3 to 19.4 x 10^3 cells/mm^3, he is febrile, and he has an increased amount of tan-colored endotracheal secretions. His renal and hepatic function are normal, and he has no allergies. There are no unusual resistance patterns at the institution. Six months ago, A.B. was hospitalized for 2 days for knee arthroplasty, for which he received perioperative intravenous and oral antibiotic therapy without complication. He lives at home with his wife.

21. Which one of the following is the most likely cause of A.B.'s symptoms?

    A. Community-acquired pneumonia
    B. Health care–associated pneumonia (HCAP)
    C. Hospital-acquired pneumonia (HAP)
    D. Ventilator-associated pneumonia (VAP)

22. Which one of the following is the best empiric treatment to recommend for A.B.?

    A. Vancomycin plus meropenem plus cefepime
    B. Vancomycin plus piperacillin/tazobactam plus ciprofloxacin
    C. Linezolid plus cefepime plus ertapenem
    D. Linezolid plus cefoxitin plus levofloxacin

23. On Day 8 of A.B.'s hospitalization, the sputum culture returns positive for extended spectrum β-lactamase (ESBL)-negative *Serratia marcescens*. The organism is reported to be susceptible to ceftriaxone, cefepime, piperacillin/tazobactam, meropenem, gentamicin, tobramycin, amikacin, ciprofloxacin, levofloxacin, and aztreonam. Which one of the following is best to recommend for A.B.?

    A. Ceftriaxone
    B. Meropenem
    C. Cefepime plus ciprofloxacin
    D. Vancomycin plus levofloxacin

24. Administrators are interested in reducing the incidence of VAP in your institution. Which one of the following parts of the Institute for Healthcare Improvement ventilator bundle is best to recommend?

    A. Chlorhexidine gluconate oral care
    B. Selective oropharyngeal decontamination
    C. Oral probiotics
    D. Stress-ulcer prophylaxis

25. A 71-year-old man is admitted for acute decompensated heart failure requiring intubation and mechanical ventilation. On day 5 of hospitalization and mechanical ventilation, he receives a diagnosis of VAP. He is empirically initiated on vancomycin, cefepime, and levofloxacin according to the institution's antibiogram. Which one of the following is best to recommend for this patient's antibiotic dosing?

    A. Follow the "start low, go slow" method, starting with the minimum doses of each antibiotic.
    B. The cefepime should be dosed to maximize the peak/MIC ratio.
    C. The levofloxacin should be dosed to maximize time above the MIC.
    D. The empiric dosing should be aggressive.

Questions 26 and 27 pertain to the following case.

C.D. is a 67-year-old woman who is admitted to the hospital for a heart failure exacerbation. She has not been hospitalized in the past year. Her medical history includes stage 3 chronic kidney disease. On day 5 of hospitalization, C.D. is febrile, has an increased WBC, and chest radiography reveals a new infiltrate in her right middle lobe. Later that same day, she experiences respiratory distress, is intubated and placed on mechanical ventilation, and is sent to the medical ICU.

26. Which one of the following is the most likely cause of C.D.'s symptoms?

    A. HCAP
    B. HAP
    C. VAP
    D. Both HAP and VAP

27. Which one of the following is best to recommend as an empiric treatment for C.D.?

    A. Vancomycin plus meropenem plus ceftazidime
    B. Vancomycin plus piperacillin/tazobactam plus gentamicin
    C. Linezolid plus piperacillin/tazobactam plus levofloxacin
    D. Linezolid plus imipenem/cilastatin plus tobramycin

28. A physician asks you about using extended-interval dosed tobramycin for the definitive treatment of *P. aeruginosa* VAP and bacteremia in a 52-year-old man. The patient has no other significant comorbidities. Which one of the following is best to recommend for this patient?

    A. Tobramycin in combination with vancomycin or linezolid
    B. Tobramycin in combination with another antipseudomonal agent.

C. Traditional dosing, not extended-interval dosing
D. A fluoroquinolone, not an aminoglycoside

29. Which one of the following best justifies the addition of aerosolized colistin to a patient's regimen for VAP?

A. Overcoming resistance of MDR/extensively drug resistant bacteria
B. Elimination of adverse effects
C. Ease of administration
D. Increased drug concentration at the infection site

30. A 52-year-old woman with advanced ovarian cancer is admitted for radical surgical debulking. She just completed a 10-day course of piperacillin/tazobactam for a presumed wound infection that was culture negative. On day 15 in the surgical ICU, she is diagnosed by bronchoalveolar lavage with *A. baumannii* VAP. Susceptibilities are not yet available, but there has been an outbreak of extensively drug resistant *A. baumannii* the last 3 months in the surgical ICU. The patient is hypotensive and tachycardic, and her urine output has been 20 mL/hour for the past 6 hours. Her WBC has increased from 9.3 x 10^3 cells/mm^3 to 17.6 x 10^3 cells/mm^3 today, and her temperature is 39.7°C. Which one of the following is best to recommend for this patient's VAP?

A. Use intravenous antibiotics only; aerosolized antibiotics are of no benefit and increase the likelihood of toxicity.
B. Hold further antibiotic therapy, pending final susceptibilities, because she just finished a course of antibiotics.
C. Start ampicillin/sulbactam as part of combination therapy because sulbactam is often active against *Acinetobacter* spp.
D. Start ceftaroline with aerosolized colistin to maximize the possibility of covering the *A. baumannii*, in case it is an extensively drug resistant strain.

31. A 47-year-old man with a medical history of type 1 diabetes is admitted for a left-sided above-the-knee amputation for necrotizing fasciitis. He received 3 days of ciprofloxacin and metronidazole intravenously beginning on the day of admission, continuing through post-operative day 2. On hospital day 3 (post-operative day 2), he is found to be in respiratory distress, is intubated, placed on a ventilator and transferred to the ICU. On hospital day 6 (ventilator day 3), his respiratory condition deteriorates further. Chest radiography is remarkable for complete whiteout in the left upper lobe and part of the left lower lobe. The patient is now febrile and has a leukocytosis with greater than 10% immature band forms. The physician would like to start tigecycline. Which one of the following is best to recommend regarding tigecycline use in this patient?

A. Monotherapy would be a good first choice for HAP/VAP.
B. It is not active against methicillin-resistant *Staphylococcus aureus* (MRSA), and vancomycin or linezolid should be added to the tigecycline therapy.
C. If used in combination with an aminoglycoside for double-coverage of gram-negative pathogens, it would be a good option.
D. It is indicated for community-acquired pneumonia but may be inferior to other agents in HAP/VAP, and should not be recommended.

32. Which one of the following is most important to consider in deciding whether to use vancomycin or linezolid in the treatment of HAP/VAP caused by MRSA?

A. The ATS/IDSA guidelines recommend linezolid ahead of vancomycin.
B. Randomized controlled studies showed a decreased mortality with linezolid.
C. Post hoc analyses of head-to-head phase III trials found vancomycin to be superior.
D. Linezolid may be a good alternative when vancomycin therapy has failed.

33. Which one of the following patients with VAP would be best treated with vancomycin instead of linezolid?

A. A patient currently receiving sertraline
B. A patient currently receiving continuous infusion dopamine
C. A patient receiving linezolid for 7 days who develops severe thrombocytopenia
D. A patient with liver enzymes increased by 25% and normal serum bilirubin and coagulation tests

34. A 48-year-old man is diagnosed with VAP. A specimen obtained by bronchoalveolar lavage shows an ESBL-positive and carbapenemase-producing *Klebsiella* spp. Which one of the following is best to recommend for this patient?

A. Ceftazidime/avibactam
B. Ceftolozane/tazobactam
C. Meropenem
D. Ampicillin/sulbactam

35. A 65-year-old man receiving mechanical ventilation in the neurosciences ICU develops a fever, leukocytosis, increased respiratory secretions, and a new infiltrate on chest radiography. Which one of the following is best to initiate for gram-positive coverage in this patient?

A. Linezolid
B. Tedizolid
C. Teicoplanin

D. Telavancin

36. A 67-year-old woman is being mechanically ventilated and empirically treated for HAP/VAP with vancomycin 750 mg intravenously every 12 hours, meropenem 1 g intravenously every 8 hours, and ciprofloxacin 400 mg intravenously every 12 hours for the past 3 days. All doses are appropriate for the patient's renal function. Sputum cultures now reveal a virtually pan-susceptible *E. coli*. Although the patient is still in the ICU on mechanical ventilation, her condition has improved since admission. Which one of the following is best to recommend regarding this patient's antibiotic treatment?

    A. Continue as above for a planned total of 8 days.
    B. Continue as above for a planned total of 15 days.
    C. De-escalate to a single agent active against the *E. coli* and continue for a total of 8 days.
    D. De-escalated to a single agent after the patient is extubated, and continue for a total of 15 days.

37. A 42-year-old man has received 5 days of cefepime therapy for suspected VAP. Vancomycin was discontinued on day 3 of therapy when the sputum Gram stain and culture were negative for any gram-positive organisms. Tobramycin was discontinued yesterday because of an increasing SCr. Sputum culture and susceptibility results are positive for *P. aeruginosa* susceptible to cefepime. Urine and blood cultures are negative. The patient has improved clinically and is now extubated. Which one of the following is best to recommend for this patient?

    A. Continue cefepime for 8 more days beyond the date of final culture and susceptibility results.
    B. Continue cefepime for a total of 8 days and monitor for recurrent infection.
    C. Continue cefepime for a total of 21 days.
    D. Add levofloxacin to the cefepime and continue antibiotics for a total of 8 days.

Questions 38 and 39 pertain to the following case.

K.L., a 60-year-old man, has been in the ICU for almost 3 weeks. He has been receiving vancomycin (dosed per the pharmacokinetics consult service), meropenem 1 g every 8 hours intravenously, and levofloxacin 750 mg once daily intravenously for 3 days for a suspected VAP. K.L. has good renal and hepatic function. His condition has worsened during the past 48 hours, and a sputum culture is positive for *Acinetobacter* spp., with susceptibilities pending.

38. Which one of the following best explains K.L.'s worsening condition?

    A. The meropenem dose is subtherapeutic.
    B. The *Acinetobacter* spp. is MDR and not susceptible to current therapy.
    C. Levofloxacin is not an ideal choice for empiric treatment.
    D. The antibiotics have not had enough time to effect an improvement in his condition.

39. Which one of the following modifications is the best to recommend for K.L.?

    A. Increase the meropenem dose.
    B. Discontinue meropenem; start ceftolozane/tazobactam.
    C. Change the levofloxacin to ciprofloxacin.
    D. Add colistin, intravenously and/or inhaled.

40. Which one of the following best justifies the use of combination therapy in an immunocompetent patient with HAP/VAP?

    A. Definitive therapy for gram-negative bacteria
    B. Definitive therapy for gram-positive bacteria
    C. Broader coverage in empiric therapy to increase chances of adequate therapy
    D. Addition of antifungal and/or antiviral agents

Learner Chapter Evaluation: HAP/VAP.

As you take the posttest for this chapter, also evaluate the material's quality and usefulness, as well as the achievement of learning objectives. Rate each item using this 5-point scale:

- Strongly agree
- Agree
- Neutral
- Disagree
- Strongly disagree

19. The content of the chapter met my educational needs.
20. The content of the chapter satisfied my expectations.
21. The author presented the chapter content effectively.
22. The content of the chapter was relevant to my practice and presented at the appropriate depth and scope.
23. The content of the chapter was objective and balanced.
24. The content of the chapter is free of bias, promotion, or advertisement of commercial products.
25. The content of the chapter was useful to me.
26. The teaching and learning methods used in the chapter were effective.
27. The active learning methods used in the chapter were effective.
28. The learning assessment activities used in the chapter were effective.
29. The chapter was effective overall.

Use the 5-point scale to indicate whether this chapter prepared you to accomplish the following learning objectives:

30. Evaluate recent literature and current guidelines on the risk factors and management of hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP).
31. Develop measures to prevent HAP and VAP, as well as complications associated with prolonged mechanical ventilation in the ICU.
32. Using key pharmacokinetic and pharmacodynamic principles, as well as individual patient information, design an appropriate regimen for the management of HAP/VAP.
33. Distinguish common multidrug resistant HAP/VAP pathogens and recommend potential antimicrobials for treatment.
34. Please provide any specific comments related to any perceptions of bias, promotion, or advertisement of commercial products.
35. Please expand on any of your above responses, and/or provide any additional comments regarding this chapter:

Other Common Infections in the ICU

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LEARNING OBJECTIVES

1. Design pharmacotherapy for catheter-associated bloodstream infections in the ICU based on patient characteristics, epidemiology, clinical presentation, and guideline-based recommendations.
2. Design pharmacotherapy for urinary tract infections in the ICU based on patient characteristics, epidemiology, clinical presentation, and evidence-based recommendations.
3. Design pharmacotherapy for intra-abdominal infections in the ICU based on patient characteristics, epidemiology, clinical presentation, and evidence-based recommendations.
4. Design pharmacotherapy for skin and soft tissue infections in the ICU based on patient characteristics, epidemiology, clinical presentation, and evidence-based recommendations.
5. Design pharmacotherapy for community-acquired pneumonia requiring ICU admission based on patient characteristics, epidemiology, clinical presentation, and evidence-based recommendations.
6. Design pharmacotherapy for CNS infections in the ICU based on patient characteristics, epidemiology, clinical presentation, and evidence-based recommendations.

ABBREVIATIONS IN THIS CHAPTER

ASB	Asymptomatic bacteriuria
CA-ASB	Catheter-associated asymptomatic bacteriuria
CABSI	Catheter-associated bloodstream infection
CAP	Community-acquired pneumonia
CA-UTI	Catheter-associated urinary tract infection
LP	Lumbar puncture
MDR	Multidrug resistant
MRSA	Methicillin-resistant *Staphylococcus aureus*
SSTI	Skin and soft tissue infection

INTRODUCTION

Managing infections is an important role for the critical care pharmacist. Antimicrobial resistance continues to rise, and few novel antimicrobial agents are on track for FDA approval, especially those targeting multidrug resistant (MDR) gram-negative infections such as *Pseudomonas aeruginosa* or carbapenem-resistant Enterobacteriaceae. Initial inappropriate antibiotic selection leads to increased mortality in patients with septic shock. Pharmacists are an important source for empiric antimicrobial recommendations in critically ill patients, including those presenting to the ED. This chapter focuses on the management of common infections.

CHALLENGES OF TREATING INFECTIONS IN THE ICU

Caring for the infected critically ill patient presents its own unique set of challenges. Adequate source control remains one of the foremost measures to cure patients in addition to antimicrobial therapy. Penetration of most antimicrobials is limited with abscesses or confined fluid collections.

Critically ill patients often have complicated pharmacokinetics/pharmacodynamics. Aggressive volume resuscitation leading to increased volume of distribution necessitates increased dosing in

the initial treatment of the patient with sepsis. Dosing during the initial 24–48 hours should be aggressive to ensure appropriate concentrations of antimicrobial, with close monitoring of renal function in patients who do not respond to initial volume resuscitation and have acute kidney injury. Renal function can change rapidly in critically ill patients, requiring frequent reassessment and subsequent dose adjustments.

CATHETER-ASSOCIATED BLOODSTREAM INFECTION

Catheter-associated bloodstream infections (CABSIs) are common in patients in the ICU, with almost 80,000 cases occurring each year in the United States. These infections produce significant morbidity, longer hospital stays, and increased mortality. The factors involved in developing a CABSI are listed in Box 3-1. Many facilities have implemented aggressive prevention strategies that have decreased the incidence of central line–associated bloodstream infections. Central line–associated bloodstream infection is often used by the National Healthcare Safety Network to denote central line infection for purposes of surveillance. Sometimes the term *catheter-related bloodstream infections* is used because catheters other than central lines (e.g., arterial lines) may also become infected, and this term usually applies to the treatment of these infections. These different terms are often used interchangeably in clinical practice.

Box 3-1. Risk Factors for Catheter-Associated Bloodstream Infection

- Type of intravascular device
- Frequency of catheter access
- Education and experience of catheter instiller
- Femoral or internal jugular insertion site
- Duration of catheter placement
- Compliance with prevention strategies

BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:

- Basic mechanisms of action, common adverse effects, and spectrum of activity of agents used to treat these infections
- Common tests used to make definitive diagnoses of these infections
- Infection control and prevention measures associated with pathogens responsible for these infections

ADDITIONAL READINGS

The following free resources have additional background information on this topic:

- National Institute of Diabetes and Digestive and Kidney Diseases. Urinary Tract Infections in Adults.
- CDC. Catheter-Associated Urinary Tract Infections.
- National Institute of Diabetes and Digestive and Kidney Diseases. Pancreatitis.
- U.S. National Library of Medicine. Peritonitis.
- CDC. Meningitis.
- CDC. Bloodstream Infection Event (Central Line–Associated Bloodstream Infection and Non–Central Line–Associated Bloodstream Infection).

Diagnosis

The diagnosis of a CABSI may be confirmed through many measures. An important principle in diagnosis is obtaining blood cultures before antimicrobial therapy to increase the yield of bacterial growth. However, antimicrobial therapy should not be delayed. Blood cultures should be obtained using recommended techniques to prevent contamination; these techniques include using chlorhexidine or an iodine preparation and allowing appropriate contact and drying time. Moreover, once cultures are obtained, blood culture bottles should be labeled with the site of accession to determine whether cultures were obtained from the correct sites and thus establish the diagnosis of CABSI.

Catheter Cultures/Blood Cultures

For epidemiologic purposes, the CDC terms a central line–associated bloodstream infection as a *primary bloodstream infection* in a patient who has a central line within 48 hours before developing a bloodstream infection without an alternative infection source. Regarding treatment, the Infectious Diseases Society of America (IDSA) guidelines recommend that a definitive diagnosis of CABSI is best made by documenting the same organism growing from both the catheter (e.g., catheter tip) and the percutaneously obtained blood culture. Alternatively, a quantitative culture of at least a 3-fold greater colony count from one catheter blood culture than the other makes the diagnosis. This is rarely done in clinical practice because time to positivity is a more practical method of diagnosis. If the central line blood culture documents growth of the same organism 2 hours or more before the peripherally obtained blood culture, the diagnosis of CABSI can be made. Feasibility of this method may be difficult, depending on documentation practices.

Rapid Diagnostics

Rapid diagnostic testing of blood cultures decreases morbidity and mortality. A comprehensive discussion of options for rapid testing is beyond the scope of this chapter, but most can

identify a gram-positive, gram-negative, or fungal pathogen within 2–3 hours after initial growth is identified (Goff 2012). These testing modalities have shown cost savings only when a dedicated provider, such as a pharmacist, communicates the rapid diagnostic results directly to the provider for intervention. Time to antimicrobial susceptibility testing is not shortened with rapid diagnostic testing.

General Management Strategies

Short-term Central Venous Catheter or Arterial Catheter

Catheter-associated bloodstream infections occurring in the ICU vary widely according to the individual center's practice, but many short-term central venous catheters are placed in the normal treatment of ICU patients. The IDSA guidelines define short-term catheters as those in use for 14 days or less. Every attempt should be made to remove short-term catheters or arterial catheters to provide adequate source control.

Long-term Central Venous Catheter or Port

Long-term catheter infections with *Staphylococcus aureus*, gram-negative bacilli, fungi, mycobacteria, or *Enterococcus* spp. usually require catheter removal. Other characteristics that indicate catheter removal include suppurative thrombophlebitis, endocarditis, severe sepsis or septic shock, and any infecting organism that remains in the bloodstream 72 hours or more after appropriate antimicrobial therapy.

Antibiotic Lock Therapy

Antibiotic lock therapy is used in the treatment of catheter-associated bloodstream infections when catheter preservation is warranted such as for catheters used for hemodialysis, cancer chemotherapy, or home parenteral nutrition.

Antibiotic lock therapy uses high concentrations of antimicrobials instilled in the catheter to "dwell." Antibiotic lock therapy is used as adjunctive therapy with systemic administration of antimicrobial therapy through the offending catheter in treating CABSIs involving coagulase-negative staphylococci and, in rare circumstances, enterococcal or gram-negative bacilli. Concomitant heparin may be instilled as well, depending on the type of catheter requiring antibiotic lock therapy. Box 3-2 lists several potential options for antibiotic lock therapy.

Empiric Therapy Recommendations

Empiric therapy should consist of antimicrobials with good activity against *Staphylococcus* and *Streptococcus* spp., including methicillin-resistant *S. aureus* (MRSA) in most cases. Gram-negative coverage with dual antipseudomonal agents is recommended in patients with severe sepsis/septic shock or in patients with neutropenia. Antifungal coverage should be provided to patients with current parenteral nutrition therapy, neutropenia, *Candida* colonization at multiple sites, or femoral catheter involvement.

Box 3-2. Selected Antibiotic Lock Therapy Solutions with Confirmed Stability and Compatibility[a]

- Cefazolin 5 mg/mL + heparin 5000 units/mL
- Daptomycin 1 mg/mL + heparin 5000 units/mL
- Gentamicin 5 mg/mL ± heparin 5000 units/mL
- Vancomycin 2 mg/mL + heparin 2500 units/mL

[a]All solutions should be mixed in normal saline except for daptomycin, which requires lactated Ringer solution for optimal activity because of the calcium requirement.

Information from Bookstaver PB, Rokas KEE, Norris LB, et al. Stability and compatibility of antimicrobial lock solutions. Am J Health Syst Pharm 2013;70:2185-98.

Pathogen-Specific Recommendations

S. aureus

S. aureus remains one of the primary pathogens in CABSIs warranting empiric coverage. Given that national rates of MRSA are generally greater than 50%, empiric coverage for MRSA should be given. Potential options for therapy are listed in Table 3-1. If methicillin-susceptible *S. aureus* is identified, de-escalation to a β-lactam with good antistaphylococcal activity and documentation of positive clinical outcomes (e.g., nafcillin, cefazolin) for patients without a severe allergy should be done. Clearance of bacteremia should be documented through surveillance blood cultures obtained at 48- to 72-hour intervals after initiation of effective antimicrobial therapy. Therapy duration in uncomplicated cases (e.g., no metastatic site of infection, no prosthetic devices) is 2 weeks and, in complicated cases, 4–6 weeks.

Coagulase-Negative Staphylococci

Coagulase-negative staphylococci are the most common cause of CABSI. Because coagulase-negative staphylococci are a common contaminant of blood cultures, the CDC defines bacteremia as when two or more bottles are positive with coagulase-negative staphylococci. Nationally, about 80% of isolates are methicillin resistant; thus, vancomycin will be the most common option. Therapy duration is generally 5–7 days after catheter removal and 10–14 days in conjunction with antibiotic lock therapy if the catheter is preserved.

Enterococci

Enterococcal CABSIs can result in significant morbidity and mortality because of their propensity to adhere to plastic surfaces. The drug of choice for treating these infections is ampicillin with or without aminoglycoside therapy. Vancomycin therapy should be reserved for patients with ampicillin-resistant strains or allergies/intolerances to penicillin therapy. Vancomycin-resistant strains should be treated with daptomycin or linezolid. Combination therapy for enterococcal CABSIs in the absence of confirmed endocarditis is

Table 3-1. Potential Options for MRSA CABSI

Antimicrobial	Normal Renal Function Dosing	Clinical Pearls
Vancomycin	15–20 mg/kg IV q8–12hr of actual body weight	Trough level goal of 15–20 mcg/mL Adjusted body weight may be needed in class II obese or higher (BMI ≥ 35 kg/m^2) Nephrotoxicity rates increased with higher trough goals and ICU stay Some evidence of vancomycin treatment failures in MICs of 2 per Etest methodology
Daptomycin	6 mg/kg IV daily of actual body weight	First-line option for vancomycin treatment failures with MRSA-complicated bacteremias Some experts recommend 8–10 mg/kg/day because of concentration-dependent killing with little additive toxicity CPK should be monitored weekly and possibly more often in renal dysfunction or in patients receiving statin therapy because signs of musculoskeletal toxicity may be masked in critically ill patients Statin discontinuation while on daptomycin requires clinical judgment depending on cardiac risk stratification Avoid in patients with concomitant pneumonia because of pulmonary surfactant inactivation
Linezolid	600 mg IV q12hr	Not FDA approved because of increased mortality in CABSI study. (This was all in patients with concomitant gram-negative infections) MRSA guidelines recommend as part of salvage therapy regimen for complicated bacteremias Bone marrow toxicity can be significant once surpassing 10–14 days of therapy Monitor for serotonin syndrome with concomitant serotonergic agents
Ceftaroline	600 mg IV q12hr	Only β-lactam with MRSA activity Not FDA approved for MRSA bloodstream infections Emerging data as frontline option for salvage therapy of complicated MRSA bacteremias with or without daptomycin Often dosed as 600 mg IV q8hr in salvage bacteremias to ensure good pharmacodynamic target attainment Has some gram-negative activity, which is a drawback for stewardship when treating purely MRSA infections
Telavancin	10 mg/kg IV daily of actual body weight	Not FDA approved for MRSA CABSIs MRSA guidelines recommend only for complicated bacteremias not responding or resistant to vancomycin or daptomycin Nephrotoxicity can be significant

CABSI = catheter-associated bloodstream infection; CPK = creatine phosphokinase; IV = intravenous(ly); MRSA = methicillin-resistant *S. aureus*; q = every.

controversial. Duration of systemic antimicrobial therapy is 7–14 days from the removal of the catheter. If the catheter is preserved, antibiotic lock therapy is given in combination with systemic antimicrobial therapy.

Gram-negative Bacilli

A variety of gram-negative bacilli may cause CABSIs. Culture and susceptibility results, including *Pseudomonas* spp., should guide definitive therapy. Monotherapy is appropriate for most patients with many agents except aminoglycosides. Therapy duration is 7–14 days after catheter removal or 10–14 days with antibiotic lock therapy.

Fungal Species

Echinocandin or azole therapy should be given depending on the pathogen identified, which is usually *Candida* spp. For a detailed discussion of therapy, see the chapter on fungal infections in the ICU.

Persistent Bloodstream Infection

Persistent bloodstream infection is a common manifestation of some CABSIs, especially those involving *S. aureus*. This can be caused by metastatic seeding of the organism into other areas. Pocket infections, orthopedic-related device infections, or endocarditis should be ruled out in patients with persistent bacteremia after catheter removal. Patients with persistent bloodstream infection in whom catheter salvage was tried in gram-negative or enterococcal CABSIs should have their catheters removed to facilitate clinical cure. For patients receiving therapy for MRSA CABSIs, clinicians should ensure that antimicrobial susceptibility has not changed during therapy because resistance has been reported in some cases.

Prevention Strategies

Most CABSIs can be prevented through proper insertion technique and site management through compliance with guideline recommendations (O'Grady 2011). When oral antimicrobial therapies can be used, placing central catheters for administration can be avoided. Recent evaluations show the superiority of universal decolonization to targeted decolonization in preventing bloodstream infections from any pathogen in the ICU. Universal decolonization was accomplished in a multicenter study using chlorhexidine daily bathing for the duration of the ICU stay and mupirocin nasal administration twice daily for 5 days (Huang 2013). Further studies are needed to confirm these findings; however, some hospitals are already adopting these practices.

URINARY TRACT INFECTIONS

Urinary tract infections (UTIs) are one of the most common bacterial infections in any health care setting. In the ICU, UTIs may be included in differential diagnoses across all spectrums of disease severity and account for a large portion of antimicrobial use. Several published guidelines pertain to the treatment of UTIs, including asymptomatic bacteriuria (ASB) (Nicolle 2005), catheter-associated UTIs (CA-UTIs) (Hooton 2010), and acute uncomplicated cystitis and pyelonephritis (Gupta 2011). However, none of these guidelines makes specific recommendations for the treatment of critically ill patients. Gram-negative bacteria are the primary causative organisms, most commonly *Escherichia coli* followed by other Enterobacteriaceae. Because the extended-spectrum β-lactamase–producing organisms are increasingly common, patient risk factors and prior culture should be evaluated and considered when selecting an empiric antimicrobial regimen (Harris 2007). The increased use of indwelling urethral catheters leads to a higher risk of developing a CA-UTI. Judicious use of these catheters is increasingly important as more performance measures and financial incentives are tied to the incidence of CA-UTIs.

Diagnosis

In the ICU setting, a wide range of UTIs may be encountered, including ASB and catheter-associated asymptomatic bacteriuria (CA-ASB), CA-UTI, and pyelonephritis. Accurate diagnosis is important to distinguish between these types of infections to determine whether treatment is appropriate and the duration of therapy. Treatment of asymptomatic UTIs is common and contributes to inappropriate antimicrobial use and subsequent resistance. A urinalysis, urine culture with Gram stain, and susceptibility should be performed in all hospitalized patients with a suspected UTI. Signs and symptoms of UTI include new-onset or worsening fever, rigors, altered mental status, lethargy, flank pain, hematuria, and suprapubic pain. Diagnosis is based on urinary study results and the presence of clinical signs and symptoms.

Catheter-Associated ASB

Catheter-associated ASB is defined as the presence of 10^3 CFU/mL or more of one or more bacterial species in a single catheter urine specimen without signs and symptoms compatible with UTI. For most patients, CA-ASB is not harmful and does not warrant treatment. Routine screening for CA-ASB to prevent the development of CA-UTI is not recommended. The treatment of CA-ASB has not been shown to decrease or prevent the progression to UTI (Nicolle 2005).

Catheter-Associated UTI

Patients with CA-UTI or pyelonephritis may or may not have some of the classic signs and symptoms associated with UTIs, which can make distinguishing between CA-ASB and CA-UTI difficult. For this reason, when a UTI is suspected, the indwelling urethral catheter must be removed or exchanged. Repeat urine studies should be obtained and used for diagnosing and identifying causative pathogens. Catheter-associated UTI is defined as the presence of 10^3 CFU/mL or more of one or more bacterial species in a single catheter urine specimen or a midstream-voided urine specimen from a patient whose catheter has been removed within 48 hours, together with the presence of signs and symptoms compatible with a UTI (Hooton 2010).

Polymicrobial infections and/or MDR organisms are common, and urine culture results are critical in determining antimicrobial therapy. After urine cultures are obtained, empiric antimicrobial therapy should be directed at the likely causative organisms given the patient's history, risk factors, any previous microbiological data or antibiotic exposure, and urinary excretion of the antimicrobial (Box 3-3). Once culture and susceptibility results are available, definitive therapy should be tailored as appropriate. Therapy duration for most critically ill patients is 7–14 days. Patients with quick symptom resolution may be treated for 7 days, whereas those with a delayed treatment response should receive 10–14 days of therapy, regardless of catheter removal (Hooton 2010).

Pyelonephritis

Although not as common as CA-UTI, pyelonephritis may be encountered in the ICU. Gram-negative bacteria remain the

Box 3-3. Common Microbiology of CA-UTI

Escherichia coli
Other Enterobacteriaceae
- *Klebsiella* spp.
- *Serratia* spp.
- *Citrobacter* spp.
- *Enterobacter* spp.

Non–lactose-fermenting gram-negative bacilli (e.g., *P. aeruginosa*)
Gram-positive cocci
- Coagulase-negative staphylococci
- *Enterococcus* spp.

Candida spp.

Information from: Hooton TM, Bradley SF, Cardenas DD, et al. Diagnosis, prevention, and treatment of catheter-associated urinary tract infection in adults: 2009 international clinical practice guidelines from the Infectious Diseases Society of America. Clin Infect Dis 2010;50:625-63.

common causative pathogens, with MDR increasing in prevalence. Critically ill patients with pyelonephritis should receive intravenous antimicrobial therapy targeted at the likely pathogen. Published guidelines for the treatment of pyelonephritis offer treatment recommendations for hospitalized patients; however, these are not ICU-specific. Preferred antibiotic treatments include the use of intravenous extended-spectrum cephalosporins or penicillins, carbapenems, aminoglycosides, or intravenous fluoroquinolones (ciprofloxacin or levofloxacin), although locally high *E. coli* resistance rates to fluoroquinolones may preclude the use of these agents empirically (Table 3-2). Empiric selection should be based on previous culture data, patient risk factors, and local resistance data. Therapy should be tailored when susceptibilities are a result. Treatment duration is typically 10–14 days (Gupta 2011). Patients receiving appropriate antibiotics who develop severe or worsening infection or persistent fever should be evaluated for possible stones, obstruction, or abscess. Urologic evaluation and imaging studies are warranted in these patients to assess the need for surgical intervention (Hooton 2012).

Prevention Strategies: Appropriate Use and Discontinuation of Indwelling Urethral Catheters

Judicious use of indwelling urethral catheters has become an important focal point in ICU care. The increased evaluation of performance measures (e.g., incidence of CA-UTI), which may

Table 3-2. Treatment Considerations for Complicated Cystitis and Pyelonephritis

Variable	Comment
Clinical spectrum	Mild cystitis to life-threatening urosepsis
Common microbiology	*Escherichia coli* (most cases) Other Enterobacteriaceae • *Klebsiella pneumoniae* Gram-positive bacteria • *Staphylococcus saprophyticus* • *Enterococcus faecalis* (may indicate contamination) • *Streptococcus agalactiae* (may indicate contamination)
Antimicrobial resistance	Fluoroquinolone and multidrug resistance common
Empiric antimicrobial treatment	Cystitis • Extended-spectrum cephalosporin, aminoglycoside, fluoroquinolone[a] (ciprofloxacin, levofloxacin) Pyelonephritis • Extended-spectrum cephalosporin ± aminoglycoside, piperacillin-tazobactam ± aminoglycoside, fluoroquinolone[a] (ciprofloxacin, levofloxacin), aminoglycoside ± ampicillin, carbapenem MRSA suspected • Add vancomycin in addition to previously listed therapy
Treatment response	Variable, may require instrumentation for cure

[a]Local fluoroquinolone resistance to *E. coli* may be high; use only if ≥ 90% susceptibility rate.

Information from: Gupta K, Hooton TM, Naber KG, et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: a 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. Clin Infect Dis 2011;52:e103-20; and Hooton T. Uncomplicated urinary tract infection. N Engl J Med 2012;366:1028-37.

Box 3-4. Indications for Indwelling Urethral Catheter Use

Appropriate

Accurate measurement of urinary output
Acute urinary retention or bladder outlet obstruction
Healing open sacral or perineal wounds
Prolonged immobilization
Perioperative use for certain surgical procedures:
- Urologic/genitourinary tract surgery
- Prolonged duration of surgery
- Intraoperative large-volume infusions or diuresis
- Intraoperative monitoring of urinary output

Comfort care/end of life

Inappropriate

Management of urinary incontinence
Means of obtaining urine culture or other diagnostic tests
Prolonged postoperative use without appropriate indication

Information from: Gould CV, Umscheid CA, Agarwal RK, et al. Guideline for Prevention of Catheter-Associated Urinary Tract Infections 2009. Atlanta: HICPAC, CDC, 2009.

be tied to financial reimbursement, has resulted in greater efforts to decrease preventable, nosocomial infections. Box 3-4 provides examples of appropriate and inappropriate uses of indwelling urethral catheters.

Indwelling urethral catheters should be removed as soon as possible to reduce the risk of CA-UTI. Some alternatives that may be considered in lieu of indwelling catheters include clean intermittent catheterization, condom catheterization in men, and portable bladder scanning, although data are inconclusive whether these techniques decrease the incidence of CA-UTI.

INTRA-ABDOMINAL INFECTIONS

Complicated intra-abdominal infections extend diffusely into the peritoneal space and are associated with either abscess formation or peritonitis. Intra-abdominal infections are one of the most commonly encountered infections in the ICU and a leading cause of infectious mortality (Solomkin 2010). Rapid diagnosis, evaluation for surgical intervention and/or source control, and antimicrobial therapy are critical to improve patient outcomes and decrease mortality.

Typically, the peritoneal cavity contains a small amount of fluid. During an infectious process, inflammatory mediators are released, which increase vascular permeability and ultimately the amount of peritoneal fluid. As the inflammatory response increases, there is a subsequent activation of the coagulation cascade promoting fibrin formation, adhesions, and abscess formation. In addition, many nerve fibers are present in the peritoneum, which explains the severe pain that often accompanies peritonitis.

Diagnosis

Patients who present with acute-onset abdominal pain and GI dysfunction (e.g., diarrhea, vomiting, obstipation) with or without signs of inflammation should be evaluated for possible intra-abdominal infection. A detailed patient history, including medical history, any recent surgeries, and/or the presence of abdominal scars—in conjunction with a thorough physical examination—can typically identify possible differential diagnoses. Physical examination findings aid in differentiating types of intra-abdominal infections and include pain out of proportion to examination (mesenteric ischemia) and the presence of hernias (obstruction or incarceration).

Laboratory evaluation should include CBC, electrolytes, liver function tests, and lactic acid. If there is high suspicion of hepatobiliary or pancreatic causes, amylase and lipase may be added. Patients who present with hemodynamic instability or signs of impending hemodynamic collapse (e.g., abdominal rigidity, guarding, rebound tenderness) should be evaluated immediately for surgical intervention and should forgo imaging studies. Other patients should undergo radiographic imaging studies, typically CT scan with oral and intravenous contrast, to determine the presence and source of infection. Oral contrast can distinguish loops of bowel from fluid collections and can help identify areas for fluid drainage. Intravenous contrast defines inflammation, hemorrhage, and abscess walls. The only exception is if a biliary cause is suspected, in which case right upper quadrant ultrasonography is more helpful for diagnosis.

Patients presenting with community-acquired intra-abdominal infections do not need microbiological evaluation because treatment is guided by risk factors and clinical symptoms. Blood cultures and Gram stains of infected material do not yield clinically relevant information in these patients. However, in areas with significant antimicrobial resistance, culture and susceptibility data should be obtained. In patients with health care–associated intra-abdominal infections, blood cultures and Gram stain of infected material are helpful.

Peritonitis can be classified as primary, secondary, or tertiary depending on clinical and microbiological features (Table 3-3).

Treatment and Therapy Duration

Restoring hemodynamic stability, decreasing or eliminating infectious foci, and eradicating pathologic organisms are the three goals of treatment. Fluid resuscitation is required for most patients, even those who are hemodynamically stable, because of intravascular volume loss. Patients with septic shock should immediately be resuscitated, according to the Surviving Sepsis Campaign guidelines (Dellinger 2012). Source control is recommended for most patients.

Empiric antimicrobial regimens should be initiated with high clinical suspicion or diagnosis of intra-abdominal infections according to the likely causative pathogen and local

Table 3-3. Classification and Clinical Features of Peritonitis

	Primary	Secondary	Tertiary
Definition	Spontaneous bacterial peritonitis, arises in absence of breach of peritoneal cavity or GI tract	Outflow of gut organisms through hole in GI tract or necrotic gut wall	Persistent or recurrent peritonitis at least 48 hours after adequate management
Infection	Monomicrobial	Polymicrobial	Polymicrobial
Microbiology	Gram-negative bacteria • *Escherichia coli* • *Klebsiella* sp. Gram-positive bacteria • *S. aureus* • *Enterococcus* sp.	Gram-negative bacteria • *E. coli* • *Enterobacter* sp. • *Klebsiella* sp. • *Proteus* sp. Gram-positive bacteria • *Enterococcus* sp. • *Streptococcus* sp. • *Staphylococcus* sp. Anaerobic bacteria • *Bacteroides* sp. • *Clostridium* sp. Fungi	Gram-negative bacteria • *Pseudomonas* sp. • *Enterobacter* sp. • *Acinetobacter* sp. Gram-positive bacteria • *Enterococcus* • Coagulase-negative staphylococci Fungi • *Candida* sp.
Clinical presentation	Minimal physical findings; acute deterioration in stable advanced liver disease	Abdominal pain and tenderness; older adult, immunocompromised, corticosteroids, or altered mental status may not have overt clinical signs	N/A
Treatment modality	Systemic antimicrobials	Surgical source control and systemic antimicrobials	Surgical source control and systemic antimicrobials (although may not alter clinical course), optimal strategy unknown

Information from: Marshall JC, Innes M. Intensive care unit management of intra-abdominal infection. Crit Care Med 2003;31:2228-37.

susceptibilities (Table 3-4, Table 3-5). Because of increasing *E. coli* resistance rates to ampicillin/sulbactam and fluoroquinolone antibiotics, these antibiotics should only be used as empiric therapy if local susceptibility patterns have greater than 90% susceptibility rates. In areas with high rates of MDR organisms, combination therapy with an aminoglycoside or polymyxin may be necessary. Adequate drug concentrations should be maintained during source control interventions, which may necessitate additional doses before a procedure (Solomkin 2010). As culture and susceptibility data become available, antimicrobial regimens should be tailored as appropriate.

Antifungal therapy should only be initiated when intra-abdominal cultures reveal *Candida* spp. Fluconazole is the drug of choice for infections caused by *Candida albicans*. An echinocandin is appropriate for infections caused by fluconazole-resistant *Candida* spp. or for initial therapy in critically ill patients (Solomkin 2010).

Typically, antimicrobial therapy for complicated intra-abdominal infections should be confined to 4–7 days if adequate source control is achieved (Sawyer 2015). Longer therapy durations may be needed if source control proves difficult. Antimicrobial therapy for acute appendicitis without evidence of rupture should be limited to 24 hours (Solomkin 2010).

Source Control

Source control is the cornerstone of therapy for intra-abdominal infections. Without achieving adequate source control, even treatment with appropriate antimicrobials often leads to recurrent infection or poor clinical outcomes.

Three main techniques are used for source control: drainage, debridement, and definitive management. Drainage aims to remove the focus of infection outside the body through conversion of an abscess to a controlled sinus or fistula. Drainage may be achieved through one of two techniques: open surgical or percutaneous intervention. Percutaneous drainage may be most appropriate for localized fluid collections, whereas open surgical drainage may be better for poorly localized, loculated, diffuse fluid collections;

Table 3-4. Empiric Antimicrobial Treatment for Community-Acquired Intra-abdominal Infections

Infection	Antimicrobial Regimen
Extra-biliary	
Perforated or abscessed appendicitis and other infections (mild to moderate severity)	Single agent: • Cefoxitin, ertapenem, moxifloxacin, tigecycline, or ticarcillin/clavulanic acid OR In combination with metronidazole: • Cefazolin, cefuroxime, ceftriaxone, cefotaxime, ciprofloxacin,[a] or levofloxacin[a]
High risk or severity: severe physiologic disturbance, advanced age, immunocompromised	Single agent: • Piperacillin/tazobactam, imipenem/cilastatin, meropenem, or doripenem OR In combination with metronidazole: • Cefepime, ceftazidime, ciprofloxacin,[a] or levofloxacin[a]
Biliary Infection	
Acute cholecystitis (mild to moderate severity)	Cefazolin, cefuroxime, or ceftriaxone
Acute cholecystitis (severe physiologic disturbance, advanced age, immunocompromised)	Piperacillin/tazobactam, imipenem/cilastatin, meropenem, or doripenem OR In combination with metronidazole: • Cefepime, ciprofloxacin,[a] or levofloxacin[a]
Acute cholangitis after bilioenteric anastomosis of any severity	Piperacillin/tazobactam, imipenem/cilastatin, meropenem, or doripenem OR In combination with metronidazole: • Cefepime, ciprofloxacin,[a] or levofloxacin[a]

[a]Local fluoroquinolone resistance to *E. coli* may be high; use only if ≥ 90% susceptibility rate.

Information from: Solomkin JS, Mazuski JE, Bradley JS, et al. Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. Clin Infect Dis 2010;50:133-64.

presence of necrotic tissue; or inability or failure of percutaneous methods. Debridement involves the physical removal of infected or necrotic solid tissue. Definitive measures are used to remove infectious foci and restore normal function and structure, typically through excision of infected or necrotic tissue. The most appropriate means for source control is determined with respect to patient-specific risk factors, source of infection, severity of illness, and hemodynamic stability.

Treatment Failure

Patients for whom adequate source control is not initially achieved are at high risk of treatment failure (Box 3-5). Patients with ongoing or recurrent clinical signs of infection after receiving 4–7 days of adequate therapy should be reevaluated. Evaluation should include reimaging studies (repeat CT scan or ultrasonography) to identify new or ongoing areas for source control intervention. New culture data should also be obtained to evaluate emerging resistant pathogens. Antimicrobial therapy should be continued and adjusted as new data become available. Other causes of fever and leukocytosis should be investigated as well, including pneumonia, UTI, *Clostridium difficile* colitis, and venous thromboembolism.

Acute Pancreatitis

One subset of intra-abdominal infections that are commonly seen in the ICU and that deserve special mention is acute pancreatitis. These patients typically present with severe, constant, radiating epigastric or left upper quadrant pain. Diagnoses are made by the presence of two of the following three criteria: abdominal pain consistent with the disease, serum amylase and/or lipase greater than 3 times the upper limit of normal, and/or characteristic findings noted on

Table 3-5. Empiric Antimicrobial Treatment for Health Care–Associated Intra-abdominal Infections

Infection	Antimicrobial Regimen
Local Susceptibility	
< 20% resistant *P. aeruginosa*, ESBL-producing Enterobacteriaceae, *Acinetobacter*, or other MDR GNB	Piperacillin/tazobactam, imipenem/cilastatin, meropenem, or doripenem OR In combination with metronidazole: • Ceftazidime, cefepime
ESBL-producing Enterobacteriaceae	Piperacillin/tazobactam, aminoglycoside, imipenem-cilastatin, meropenem, or doripenem
P. aeruginosa > 20% resistance to ceftazidime	Imipenem/cilastatin, meropenem, doripenem, piperacillin/tazobactam, aminoglycoside, or polymyxin
MRSA suspected (known colonization, prior treatment failure, significant antibiotic exposure)	Vancomycin
Biliary Infection	
Any severity	In combination with vancomycin: • Piperacillin/tazobactam, imipenem/cilastatin, meropenem, or doripenem OR In combination with vancomycin and metronidazole: • Cefepime, ciprofloxacin,[a] or levofloxacin[a]

[a]Local fluoroquinolone resistance to *E. coli* may be high; use only if ≥ 90% susceptibility rate.

ESBL = extended-spectrum β-lactamase; GNB = gram-negative bacilli; MDR = multidrug resistant.

Information from: Solomkin JS, Mazuski JE, Bradley JS, et al. Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. Clin Infect Dis 2010;50:133-64.

Box 3-5. Predictive Factors for Inadequate Source Control

- Delay > 24 hours in initial intervention
- High severity of illness (APACHE II score ≥ 15)
- Advanced age
- Comorbidities and degree of organ dysfunction
- Low albumin concentration
- Poor nutritional status
- Degree of peritoneal involvement or diffuse peritonitis
- Inability to achieve adequate debridement or drainage control

APACHE = Acute Physiology and Chronic Health Evaluation.

Information from: Solomkin JS, Mazuski JE, Bradley JS, et al. Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. Clin Infect Dis 2010;50:133-64.

radiographic imaging studies. Transabdominal ultrasonography may be helpful in determining the etiology. The most common causes are gallstones and alcohol. Other less common causes include hypertriglyceridemia and pancreatic tumor.

Similar to other intra-abdominal infections, initial management is aimed at fluid resuscitation and restoration of hemodynamic stability. Patients with acute pancreatitis complicated by biliary sepsis may benefit from early endoscopic retrograde cholangiopancreatography (ERCP). However, in patients without evidence of biliary obstruction or those with mild disease, ERCP is unwarranted (Tenner 2013).

The use of antimicrobial therapy in necrotizing pancreatitis is controversial. The use of prophylactic antibiotics in patients with severe acute pancreatitis or in patients with sterile necrosis is not recommended. The role of antimicrobials appears to be better served in the treatment of established infection. Infectious necrotizing pancreatitis should be suspected in patients with decompensation or who have little improvement after 7–10 days of hospitalization. These patients should receive prompt antimicrobial therapy with agents known to penetrate the pancreas (carbapenems, fluoroquinolones, and metronidazole) because antibiotic therapy delays or decreases the need for invasive intervention. The routine addition of antifungal agents is not recommended (Tenner 2013).

SKIN AND SOFT TISSUE INFECTIONS

Although most patients with skin and soft tissue infections (SSTIs) are treated as outpatients, some are treated in the inpatient setting, including the ICU. Guidelines regarding SSTI management in general were recently updated in 2014 but do not specifically delineate treatment in critically ill patients (Stevens 2014). The FDA recently defined an acute bacterial skin/skin structure infection as one of the following three infections: (1) cellulitis/erysipelas, (2) wound infection, or (3) major cutaneous abscess. Each of these must possess a minimum lesion of 75 cm^2. Specific data regarding the incidence of admission of patients with SSTIs to the ICU, as well as a breakdown of the type of SSTI, are not readily available. An analysis showed that about 9% of patients with SSTIs admitted to the hospital require ICU admission (Shen 2010).

Certain characteristics of SSTIs may lead to ICU admission. Risk factors associated with bacteremia caused by an SSTI include fever, hypotension, and central line on presentation (Jenkins 2010). Patients who are neutropenic also have increased risk of bacteremia and may require ICU admission. Any patient with potential necrotizing fasciitis will require ICU management with early consultation to surgery for acute management. Many patients present to the ICU because of an SSTI but also develop a less severe SSTI while in the ICU.

Source control for wound infections and major abscesses remains imperative for definitive management. Antimicrobial treatment without proper source control leads to significant clinical failures. Proper source control includes debridement and drainage for wound infections, as well as incision and drainage for major abscesses. In necrotizing fasciitis, urgent consultation with surgery is a necessity for potential debridement and even amputation to decrease mortality.

Major Cutaneous Abscesses

Management of purulent SSTIs such as major abscesses, carbuncles, or furuncles that require ICU admission should consist of appropriate incision and drainage plus antimicrobial therapy. The primary pathogens usually involved are gram positive, with *S. aureus* as the predominant pathogen. Methicillin-resistant *S. aureus* (MRSA) rates remain above 50% in many areas of the United States, so empiric therapy should focus on treating MRSA. Local susceptibility rates should be used to determine MRSA susceptibility rates to help guide empiric therapy for SSTIs.

Many agents have FDA label approval for SSTIs because this is often the initial indication for many antimicrobials. Suitable initial options include vancomycin, clindamycin, daptomycin, linezolid, ceftaroline, and telavancin. Newly approved agents include tedizolid, dalbavancin, and oritavancin. Data are unavailable regarding the treatment of SSTIs in critically ill patients with these newly approved drugs, and treatment with these agents is not currently recommended. Dalbavancin and oritavancin have more of a role in the outpatient treatment of SSTIs because they have prolonged half-lives (greater than 200 hours). Caution with clindamycin should be exercised because MRSA susceptibility rates can vary widely across geographic regions. Clindamycin should not be used empirically in adults where susceptibility rates are less than 85%–90% (Stevens 2014). Trimethoprim/sulfamethoxazole, as well as tetracyclines such as doxycycline should be reserved for the treatment of outpatient SSTIs because data are sparse in critically ill patients.

If analyses of culture data from incision and drainage show methicillin-susceptible *S. aureus*, an antistaphylococcal penicillin such as nafcillin or a first-generation cephalosporin such as cefazolin should be used in lieu of MRSA agents.

Cellulitis/Erysipelas

Nonpurulent SSTIs are primarily caused by gram-positive pathogens, with *Streptococcus* spp. such as *S. pyogenes* representing the primary pathogens. Positive identification of an organism in nonpurulent SSTIs occurs in less than 20% of patients (Stevens 2014). In hemodynamically stable patients, therapy may be directed against *Streptococcus* spp. with agents such as nafcillin or cefazolin. However, in patients who present with hemodynamic instability, broad-spectrum coverage should be used against MRSA, *Streptococcus* spp., gram-negative bacilli, and anaerobes until necrotizing fasciitis is ruled out. De-escalation of therapy to gram-positive coverage including MRSA can occur with caution once necrotizing fasciitis is removed from the differential diagnosis.

Wound Infections

Wound infections occurring in the ICU are generally surgical site infections, which are primarily managed with suture removal plus incision and drainage (Stevens 2014). A short course of an antimicrobial with gram-positive coverage for *S. aureus* should be given for patients with surgical site infections after clean operations with systemic signs of infection. Patients at a higher risk of MRSA (e.g., known previous MRSA infection, colonization, recent hospitalization, recent antimicrobial exposure) should receive appropriate MRSA coverage such as vancomycin. Patients with infections after surgery on the axilla, female genitourinary tract, GI tract, or perineum should also receive gram-negative and anaerobic coverage.

Necrotizing Soft Tissue Infections

Necrotizing skin infections carry the highest mortality, with estimates of 25%–35%. High suspicion of necrotizing skin infection is crucial for early surgical intervention because mortality is associated with a delay in diagnosis. Identified risk factors include immunosuppression, diabetes mellitus, obesity, and intravenous drug use (Hussein 2013).

Diagnosis is difficult, with the most specific findings of necrotizing skin infections being skin necrosis, crepitans, bullae, gas on imaging, and hemodynamic instability, which generally occur late in presentation. These signs should prompt immediate surgical consultation and radiographic imaging

for potential debridement (Hussein 2013). Certain laboratory findings are helpful in differentiating necrotizing from non-necrotizing infections. In a single-center study, a WBC less than 15.4 x 10^3 cells/mm^3 or serum sodium greater than 135 mmol/L had a negative predictive value of 99%, helping to rule out a necrotizing skin infection (Wall 2000).

Although debridement is the primary therapy, broad-spectrum antimicrobial therapy should be initiated as soon as possible because necrotizing skin infections are often polymicrobial. The most common bacteria isolated include *S. pyogenes* (group A streptococci), MRSA, *Aeromonas hydrophila*, *Vibrio* spp., and *Pasteurella* spp. (Hussein 2013). Therapy should include gram-negative, anaerobic, and gram-positive coverage including MRSA. Potential first-line regimens should include vancomycin plus piperacillin/tazobactam or doripenem. Clindamycin is often given empirically because of its known exotoxin-suppressing characteristics. Clindamycin is specifically important with group A streptococci necrotizing skin infections where high inoculums of bacteria may lead to decreased effectiveness of penicillin. Hence, high-dose intravenous penicillin plus intravenous clindamycin is the regimen of choice for group A streptococci. Intravenous immunoglobulin therapy has also shown benefit in two recent reports, with a potentially enhanced benefit in invasive group A streptococci infections as well as clindamycin (Carapetis 2014; Linner 2014).

Therapy duration is determined primarily by when final debridement or potentially amputation is performed. At this point, if the patient has had significant clinical improvement and has been afebrile for 48–72 hours, antimicrobial therapy may be discontinued (Stevens 2014).

COMMUNITY-ACQUIRED PNEUMONIA

Almost 3.5 million deaths occur per year globally because of community-acquired pneumonia (CAP), making it the infectious disease with the highest mortality. Admissions for CAP often require long ICU stays and mechanical ventilator support and may result in acute respiratory distress syndrome. This syndrome can result in significant morbidity and mortality (Wunderink 2014).

Typical clinical presentation is consistent with systemic signs of infection (fever, chills, leukocytosis) together with respiratory signs/symptoms (cough, productive sputum, shortness of breath, pleuritic chest pain). A new/modified infiltrate on chest radiography or CT scan is required together with these symptoms for diagnosis of CAP.

Etiology

The most common pathogens in patients admitted to the ICU for CAP are *Streptococcus pneumoniae*, *Haemophilus influenzae*, other gram-negative bacilli, *Legionella* spp., and *S. aureus.* Primary infection or coinfection with influenza virus should be considered during the flu season. Appropriate diagnostic testing for ICU CAP includes both sputum and blood cultures, as well as urinary antigen testing for both *S. pneumoniae* and *H. influenzae* pending availability. Community-acquired MRSA should be considered in those with risk factors such as recent influenza illness, prior antibiotic therapy (especially fluoroquinolones), or injection drug use.

Antimicrobial Therapy

Pharmacists in the critical care setting as well as the ED are in an ideal position to provide appropriate empiric therapy recommendations for the treatment of ICU CAP (Kollef 1999). Antimicrobial therapy should be given within 4 hours of presentation to the ED, which often can be accomplished through availability of the most commonly used medications in automated dispensing cabinets. Appropriate regimens for the treatment of CAP in patients admitted to the ICU are listed in Box 3-6.

Community-Acquired MRSA

Community-acquired MRSA is becoming an important pathogen in CAP. Clinical presentation is sometimes severe, with ICU admission required, and complications such as empyema and necrotizing pneumonia are often present. Appropriate empiric options include vancomycin or linezolid for ICU CAP with MRSA risk factors. In patients with potential necrotizing pneumonia, linezolid monotherapy or vancomycin plus clindamycin are appropriate options because either regimen will

Box 3-6. Appropriate Empiric Regimens for ICU Community-Acquired Pneumonia

Regimen

1. Ampicillin/sulbactam 3 g IV q6hr PLUS
   azithromycin 500 mg IV daily OR
   levofloxacin 750 mg IV daily OR
   moxifloxacin 400 mg IV daily
2. Ceftriaxone 1–2 g IV daily OR
   cefotaxime 2 g IV q6hr PLUS
   azithromycin 500 mg IV daily OR
   levofloxacin 750 mg IV daily OR
   moxifloxacin 400 mg IV daily
3. Severe penicillin allergy: levofloxacin
   750 mg IV daily OR
   moxifloxacin 400 mg IV daily PLUS
   aztreonam 2 g IV q8hr

Clinical Pearls

- Monitor QTc daily because of potential prolongation with macrolides or fluoroquinolone therapy
- Ampicillin/sulbactam or moxifloxacin may be preferred in patients with potential aspiration event
- Cephalosporin-based therapy should be considered in patients with mild penicillin allergy
- MRSA coverage should be considered in patients with known colonization, recent influenza-like illness, or hemodynamic instability
- *Pseudomonas* coverage empirically should be considered in patients with known structural lung disease or severe COPD

COPD = chronic obstructive pulmonary disease; IV = intravenously; q = every; QTc = corrected QT.

treat MRSA as well as suppress exotoxin production, which may contribute to the necrotizing features of certain strains (Liu 2011). In patients with empyema or necrotizing pneumonia, drainage procedures should be used together with antimicrobial therapy for appropriate source control.

P. aeruginosa

Although *P. aeruginosa* is a much more common pathogen in health care–associated pneumonia, hospital-acquired pneumonia, and ventilator-associated pneumonia, it can be a potential pathogen in CAP, especially in ICU-related CAP (Mandell 2007). Risk factors for infection with this pathogen include recent antimicrobial therapy, a history of severe chronic obstructive pulmonary disease exacerbation leading to common use of corticosteroids or antimicrobials, and structural lung disease. If these risk factors are present, appropriate empiric therapies should include an antipseudomonal β-lactam (piperacillin/tazobactam or cefepime or ceftazidime) plus either an aminoglycoside or an antipseudomonal fluoroquinolone (ciprofloxacin or levofloxacin). Coverage for atypical pathogens with a macrolide should also be given, as should potential MRSA therapy (vancomycin or linezolid) for patients with risk factors.

CNS INFECTIONS

Although CNS infections are less common than other infections in the ICU, rapid diagnosis and intervention is of utmost importance with this often-debilitating infection. The CNS infections most likely to present in the ICU are severe bacterial meningitis (community acquired, trauma related, or post-neurosurgical), viral encephalitis, or cryptococcal meningitis (discussed in the chapter on fungal infections in the ICU). Routine vaccination has decreased the incidence of bacterial meningitis. Rapid diagnosis and urgent administration of appropriate antimicrobial therapy remains the cornerstone of therapy. The role of adjunctive therapies, including the administration of corticosteroids and targeted temperature management, remains controversial.

Diagnosis

Because urgent intervention with appropriate antimicrobials reduces mortality and neurologic sequelae, early recognition and diagnosis is important. However, this can be challenging for clinicians because of atypical patient presentations, delayed lumbar puncture (LP), and difficulties with interpreting CSF results. Most clinicians would identify the classic triad of rash, neck stiffness, and altered mental status as clinical signs of meningitis. Recent studies have shown that this triad may not be present in all adult patients with bacterial meningitis; however, almost all patients will present with at least two of the four symptoms of headache, fever, neck stiffness, and altered mental status (Brouwer 2012).

Lumbar puncture is needed to obtain CSF for diagnostic tests; however, this may be delayed because of fear of inducing brain herniation in some patients. Lumbar puncture and subsequent removal of CSF produces a transient change in the cranial-caudal pressure gradient, resulting in displacement of cerebrum and brain stem, which may precipitate brain herniation. Cerebral herniation may also occur in patients with bacterial meningitis who do not receive LP, so the true incidence of LP-induced herniation is unknown. The routine use of CT imaging before LP is not recommended because of delayed antimicrobial initiation, resulting in increased mortality rates. However, it may be prudent to obtain CT before LP in

Patient Care Scenario

A 68-year-old man is given a diagnosis of severe CAP requiring intubation and ICU admission. Three days ago, he was seen by his primary care provider and given a 5-day course of levofloxacin for presumed CAP. His only allergy is a mild rash to amoxicillin. You are asked by the intensivist to recommend an appropriate empiric regimen.

ANSWER

Community-acquired pneumonia is one of the most common infections requiring ICU care because of hypoxic respiratory failure often requiring mechanical ventilator support. The Infectious Diseases Society of American/American Thoracic Society guidelines contain recommendations specific for ICU patients. In general, the options are a penicillin such as ampicillin/sulbactam or a third-generation cephalosporin such as ceftriaxone plus azithromycin or a "respiratory" fluoroquinolone such as levofloxacin or moxifloxacin. *Respiratory fluoroquinolone* is a confusing term that means good activity against *S. pneumoniae*, which ciprofloxacin lacks. For this patient, ampicillin/sulbactam would be inappropriate because the patient has a penicillin allergy. Levofloxacin or moxifloxacin therapy would be inappropriate because the patient was receiving this when he decompensated. Therefore, the best choice would be ceftriaxone plus azithromycin. The patient should also be assessed further for any potential risk factors for MRSA such as previous colonization or recent influenza-like illness. If any of these risk factors are present, MRSA therapy should also be administered with either vancomycin to target a serum trough concentration of 15–20 mcg/mL or linezolid.

1. Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis 2007;44:S27-42.

2. Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children. Clin Infect Dis 2011;52:e18-55.

Box 3-7. Patients Who Should Undergo Head CT before Lumbar Puncture

- New-onset seizures
- Immunocompromised state (HIV/AIDS, immunosuppressive therapy, transplantation)
- CNS lesion (mass lesion, stroke, focal infection)
- Suspected space-occupying lesion (papilledema, focal neurologic deficits, evolving signs of brain tissue shift)
- Moderate to severe altered mental status

Information from: Brouwer MC, Thwaites G, Tunkel A, et al. Dilemmas in the diagnosis of acute community-acquired bacterial meningitis. Lancet 2012;380:1684-92.

the subset of patients that may be at increased risk of brain herniation after LP (Box 3-7).

Once the LP is performed and the CSF obtained, diagnostic tests can differentiate between bacterial, viral, and fungal causes (Table 3-6). Common diagnostic tests and measurements performed include opening pressure; CSF examination (appearance, cell counts, glucose, protein); and CSF Gram stain and culture. Blood cultures should always be obtained as soon as possible and may be helpful in patients who received antimicrobials before the LP is performed. Obtaining a detailed patient history, including medical, travel, vaccination, and high-risk behaviors (recreational drug use and/or sexual history), is imperative to identify possible causative pathogens.

Bacterial Meningitis

Despite advances in care, bacterial meningitis continues to be associated with high mortality rates and significant neurologic impairment in those who survive, most notably hearing loss. The types of bacterial meningitis most likely to be seen in the ICU setting are community acquired, head trauma, post-neurosurgical, or CSF-shunt associated. Although clinical data are lacking on the relationship between time to initiation of therapy and clinical outcomes, antimicrobial therapy should be initiated as soon as possible. Empiric antibiotic regimens are based on the likely causative pathogens, incorporating patient-specific factors and underlying medical conditions (Table 3-7).

The role of adjunctive therapies, including rifampin and corticosteroid therapies, remains less clear. Rifampin should only be used in combination with standard therapy if the isolate has shown susceptibility and there is an expected delay in response. In patients with a CSF shunt infection caused by staphylococci, rifampin should be added to vancomycin, especially if shunt removal is not feasible.

Data on the use of dexamethasone for acute bacterial meningitis are conflicting, with the risks and benefits continuing to be debated. The most recent meta-analysis, which included data from adult and pediatric patients, showed benefits in associated morbidity, including reduction in the rate of hearing loss (RR 0.74; 95% CI, 0.63–0.87) and severe hearing loss (RR 0.67; 95% CI, 0.51–0.88). However, a statistically significant mortality benefit was not seen (RR 0.9; 95% CI, 0.8–1.01). Subgroup analyses for adult patients receiving dexamethasone reflected the overall results, indicating a benefit in the rate of hearing loss (RR 0.74; 95% CI, 0.56–0.98) but no mortality benefit (RR 0.74; 95% CI, 0.53–1.05). Subgroup analysis including both pediatric and adult patients with meningitis caused by *S. pneumoniae* did have a mortality benefit (RR 0.84; 95% CI, 0.72–0.98). In contrast to previous reports, a subgroup analysis did not show an efficacy difference between patients who received dexamethasone before or with the first dose of antibiotics and those who received it after the first dose of antibiotics. Of note, no harmful effects from corticosteroid administration were seen (Brouwer 2013). Given the available clinical evidence, dexamethasone 0.15 mg/kg given intravenously four times daily for 4 days should be administered to adult patients with a high clinical suspicion of or proven bacterial meningitis. Some clinicians may discontinue dexamethasone if meningitis is caused by bacteria other

Table 3-6. Typical CSF Findings in Meningitis

Test	Bacterial	Viral
Opening pressure	Elevated; 200–500 mm H_2O	Normal
WBC	Elevated; ≥1000 cells/mm^3	Normal to mild elevation; <100 cells/mm^3
Cell differential	Neutrophil predominance; ≥80%	Lymphocyte predominance
Protein	Mild to marked elevation	Normal to moderate elevation
Glucose	Decreased; <40 mg/dL	Normal
CSF/serum glucose ratio	Normal to marked decrease; ≤0.4	Normal

Information from: Tunkel AR, Hartman B, Kaplan S, et al. Practice guidelines for the management of bacterial meningitis. Clin Infect Dis 2004;39:1267-84; and Tunkel AR, Glaser CA, Bloch KC, et al. The management of encephalitis: clinical practice guidelines by the Infectious Diseases Society of America. Clin Infect Dis 2008;47:303-27.

Table 3-7. Recommendations for Empiric Antibiotics for Suspected Bacterial Meningitis

	Common Bacterial Pathogens	Antibiotic Therapy
Age		
16–50 years, immunocompetent	*Neisseria meningitidis*, *S. pneumoniae*	Vancomycin + third-generation cephalosporin[a]
> 50 years or immunocompromised (including alcoholism)	*S. pneumoniae*, *N. meningitidis*, *Listeria monocytogenes*, aerobic gram-negative bacilli	Vancomycin + third-generation cephalosporin[a] + ampicillin
Head Trauma		
Basilar skull fracture	*S. pneumoniae*, *Haemophilus influenzae*, group A β-hemolytic streptococci	Vancomycin + third-generation cephalosporin[a]
Penetrating trauma	*S. aureus*, coagulase-negative staphylococci, aerobic gram-negative bacilli (including *P. aeruginosa*)	Vancomycin + cefepime OR vancomycin + ceftazidime OR vancomycin + meropenem
Post-neurosurgery	Aerobic gram-negative bacilli (including *P. aeruginosa*), *S. aureus*, coagulase-negative staphylococci	Vancomycin + cefepime OR vancomycin + ceftazidime OR vancomycin + meropenem
CSF shunt	Coagulase-negative staphylococci, *S. aureus*, aerobic gram-negative bacilli (including *P. aeruginosa*), *Propionibacterium acnes*	Vancomycin + cefepime OR vancomycin + ceftazidime OR vancomycin + meropenem

[a]Ceftriaxone or cefotaxime.

Information from Tunkel AR, Hartman B, Kaplan S, et al. Practice guidelines for the management of bacterial meningitis. Clin Infect Dis 2004;39:1267-84. and van de Beek D, de Gans J, Tunkel A, et al. Community-acquired bacterial meningitis in adults. N Engl J Med 2006;354:44-53.

than *S. pneumoniae* because of the lack of benefit with other bacterial causes (Tunkel 2004). More recently, a trial examining the use of targeted temperature management in patients with severe bacterial meningitis to improve outcomes was terminated early because of the lack of beneficial effect and potential harm observed (Mourvillier 2013).

Once the bacterial pathogen has been isolated and susceptibility data are available, antimicrobial therapy should be de-escalated. Clinical data for the duration of treatment are lacking, and the recommendations are largely based on expert opinion. In general, infections caused by *N. meningitidis* or *H. influenzae* are treated for 7 days and for up to 2 weeks for cases caused by *S. pneumoniae*. Longer durations may be required for the treatment of *Streptococcus agalactiae* (14–21 days), aerobic gram-negative bacilli (21 days), and *Listeria monocytogenes* (greater than 3 weeks). Treatment duration should be individualized according to the patient's response.

Viral Encephalitis

The diagnosis of infectious encephalitis can be challenging because of the wide range of causative organisms. One the best ways to determine likely etiology is with a thorough patient history, including travel history, contact with individuals traveling abroad, recreational activities, contact with animals/insects, and vaccination status. Patients with encephalitis often present with seizures, which are rare with meningitis. In addition to the diagnostic tests previously discussed, other tests that may help distinguish viral causes of encephalitis include tissue biopsy, antigen detection, and nucleic acid amplification tests. Neurodiagnostic imaging studies are also an important and commonly used tool for diagnosis. The MRI is a more specific and sensitive test to evaluate encephalitis. The CT should only be used in patients when MRI is unavailable or not possible.

Although the potential causes are many, treatment options remain limited. Patients with suspected encephalitis should be treated with acyclovir (10 mg/kg of ideal body weight intravenously given every 8 hours for normal renal function) until the diagnosis is ruled out or a causative pathogen is ascertained. Once a causative pathogen is established, treatment should be tailored to target that pathogen. In the ICU setting, the most common cause of viral encephalitis is herpes simplex virus, which is treated with acyclovir. If acyclovir cannot be used or the patient has suspected or proven cytomegalovirus, alternative antivirals include ganciclovir and foscarnet. Cidofovir is not a viable alternative because clinical data regarding the ability to penetrate the blood-brain barrier are lacking (Tunkel 2008). The many other viral causes of encephalitis are outside the scope of this review.

CONCLUSION

Critical care pharmacists are extensively involved in the treatment of ICU patients with many different infections. They can provide expert pharmacotherapy recommendations for each of the common ICU infections seen on a continual basis as well as in the ED, where many of these infections are initially managed.

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Self-Assessment Questions

Questions 41 and 42 pertain to the following case.

G.B. is a 41-year-old woman (weight 83 kg) with diabetes mellitus whose last A1C (3 months ago) was 11.7%. Her medical history also includes hypertension, hyperlipidemia, and cardiac surgery (three-vessel coronary artery bypass grafting 2 years ago). She has no known drug allergies. G.B. presents to the ED about 24 hours after "popping a pimple" on the back of her neck with increasing pain, streaking erythema down her back, subjective fevers, and weakness. The redness has progressed significantly during the past 12 hours, according to patient report. Her neck pain on physical examination seems to be out of proportion to the physician's findings. Vital signs on admission include blood pressure 100/60 mm Hg, temperature 103.1°F (39.5°C), respiratory rate 30 breaths/minute, and heart rate 110 beats/minute (sinus tachycardia). Initial laboratory results also reveal acute kidney injury with an SCr of 3.0 mg/dL (baseline 1.0 mg/dL). G.B. receives a diagnosis of severe sepsis; she is initially treated with aggressive volume resuscitation and broad-spectrum antibiotics resulting in hemodynamic stability. Blood cultures are obtained and sent to the laboratory.

41. Which one of the following is the best intervention for G.B.?

    A. Do surveillance testing for methicillin-resistant *Staphylococcus aureus* (MRSA).
    B. Call general surgery for immediate consultation.
    C. Perform lumbar puncture (LP).
    D. Perform rapid diagnostics on the blood cultures.

42. G.B.'s wound and blood cultures grow group A streptococci. She remains in the ICU after surgical debridement with more debridement planned. Which one of the following antimicrobial regimens is best to recommend for G.B.?

    A. Clindamycin 900 mg intravenously every 8 hours
    B. Meropenem 1 g intravenously every 8 hours
    C. Penicillin 4 million units intravenously every 4 hours plus clindamycin 900 mg intravenously every 8 hours
    D. Penicillin 4 million units intravenously every 4 hours plus vancomycin 15 mg/kg intravenously every 12 hours

43. A patient presents to the ICU with severe sepsis from a complicated skin/skin structure infection on his left lower leg. He receives broad-spectrum antibiotic therapy, including piperacillin/tazobactam and vancomycin, as well as incision and debridement. He is now hemodynamically stable and clinically improving. His wound and blood cultures are growing methicillin-susceptible *S. aureus*. He has no known drug allergies. Which one of the following, in addition to discontinuing piperacillin/tazobactam, is best to recommend for this patient?

    A. Maintain vancomycin monotherapy.
    B. Initiate cefazolin.
    C. Initiate cefepime.
    D. Discontinue vancomycin and initiate cefazolin monotherapy.

44. A patient with no known drug allergies presents to the ED with severe community-acquired pneumonia (CAP). The team wants to initiate empiric therapy before transferring the patient to the ICU. Which one of the following, with or without vancomycin, is best to recommend for this patient?

    A. Cefpodoxime plus azithromycin
    B. Ceftriaxone plus doxycycline
    C. Ampicillin/sulbactam plus azithromycin
    D. Moxifloxacin

45. The medical ICU resident requests your assistance regarding an empiric regimen for a patient with CAP about to be transferred from the ED to the ICU for treatment. The patient has normal renal function on initial laboratory assessment and a history of an anaphylactic reaction to penicillin. Which one of the following is best to recommend for this patient?

    A. Ciprofloxacin monotherapy
    B. Moxifloxacin plus rifampin
    C. Aztreonam plus tobramycin
    D. Levofloxacin plus aztreonam

46. A 34-year-old woman with no significant medical history presents to the ICU with severe CAP in septic shock requiring intubation, aggressive volume resuscitation, and vasopressors. She reports an allergy to co-trimoxazole. She receives ceftriaxone 1 g intravenously and azithromycin 500 mg intravenously in the ED. Initial Gram stain of both sputum cultures and blood cultures 12 hours after admission reveals many gram-positive cocci in clusters. Rapid diagnostic testing of the blood cultures confirms MRSA. Which one of the following is best to add to this patient's antimicrobial regimen?

    A. Sulfamethoxazole/trimethoprim
    B. Clindamycin
    C. Daptomycin
    D. Linezolid

Questions 47 and 48 pertain to the following case.

M.T. is a 63-year-old man with no known drug allergies and a medical history significant for non-Hodgkin lymphoma. He is currently undergoing chemotherapy and presents with fever, chills, and hypotension requiring aggressive volume resuscitation. After an appropriate fluid challenge, M.T. remains hypotensive and is placed on a norepinephrine drip titrated to a mean arterial pressure of 65 mm Hg. Initial laboratory results are significant for WBC 15 x 10^3/cells/mm^3 with 30% bands. M.T. is febrile at 102.7°F (39.3°C) with a heart rate

of 100 beats/minute and respiratory rate of 30 breaths/minute. He has a peripherally inserted central catheter (PICC) for receiving blood transfusions; there is erythema around the insertion site. One month ago, M.T. was treated for a UTI with 10 days of levofloxacin. Antimicrobial therapy with piperacillin/tazobactam, tobramycin, and vancomycin is initiated in the ED.

47. Which one of the following would best optimize M.T.'s chance of clinical cure?

    A. Retain the PICC using cefazolin antibiotic lock therapy.
    B. Retain the PICC using vancomycin antibiotic lock therapy.
    C. Remove the PICC and discontinue systemic antibiotic therapy.
    D. Remove the PICC and continue systemic antibiotic therapy.

48. On M.T.'s hospital day 2, all four blood cultures obtained (two aerobic and two anaerobic) from the peripheral line and the PICC line in the ED are growing gram-positive cocci in clusters. Rapid diagnostic testing reveals MRSA, which is confirmed through culture and susceptibility testing 2 days later. On hospital day 9, M.T. is still febrile (102.3°F), and blood cultures remain positive for MRSA with a vancomycin MIC of 2 per Etest. The automated susceptibility results show that the organism is susceptible to daptomycin, linezolid, ceftaroline, and telavancin. M.T. has been receiving vancomycin since admission with troughs of 15–20 mcg/mL. Other foci of infection are being ruled out by the managing team, including a pending transesophageal echocardiogram to rule out endocarditis. Which one of the following is best to recommend for M.T.?

    A. Target vancomycin troughs of 20–25 mcg/mL.
    B. Switch vancomycin to linezolid.
    C. Switch vancomycin to telavancin.
    D. Switch vancomycin to daptomycin with or without ceftaroline.

Questions 49 and 50 pertain to the following case.

K.M., a 67-year-old man, sustains cardiac arrest on hospital day 3 requiring advanced cardiac life support; he is transferred to the ICU after return of spontaneous circulation is restored. After 1 week in the ICU, K.M. develops a new fever with subsequent workup including blood cultures (two aerobic and two anaerobic). Twenty-four hours later, both aerobic samples and one of the anaerobic samples are growing gram-positive cocci in clusters. Two culture samples were from the femoral groin central catheter placed during the cardiac code, and the other two were from a peripheral site. The central catheter's blood cultures were positive 4 hours before the peripheral site's blood cultures. The ICU resident asks for information regarding rapid diagnostic capability for K.M.'s blood cultures.

49. Which one of the following is the best response to give the resident regarding rapid diagnostic testing of K.M.'s blood cultures?

    A. It is cost-effective when a pharmacist provides the results directly to the health care team.
    B. Rapid diagnostic testing for blood cultures is limited to gram-positive pathogens only.
    C. It usually takes as much as 6–12 hours for identification from the time of initial growth.
    D. Antimicrobial susceptibility testing is available simultaneously at the time of rapid diagnosis of the pathogen.

50. K.M.'s blood cultures are identified as *Staphylococcus epidermidis* that is oxacillin resistant. The patient is clinically responding to therapy on day 3 of vancomycin. Which one of the following is best to recommend for K.M.?

    A. Maintain the central line and continue vancomycin therapy for a total of 7 days.
    B. Remove the central line and continue vancomycin therapy for a total of 7 days.
    C. Maintain the central line and continue vancomycin therapy for a total of 14 days.
    D. Remove the central line and continue vancomycin therapy for a total of 14 days.

51. A 52-year-old man who resides at a nursing home presents to the ED with left-sided weakness and altered mental status. His medical history includes diabetes mellitus, hypertension, several cerebrovascular attacks, and paraplegia. He has an indwelling urethral catheter in place since his last hospitalization. The patient was treated 3 weeks ago for a UTI after presenting with lethargy and hematuria. The nursing home staff reports that the patient has had no recent episodes of fever or pain. In the ED, the patient is hypertensive and afebrile with worsening left-sided weakness. Although he has no overt signs of infection, the physician decides that the patient needs to be pan cultured because of his altered state, chronic urethral catheter, and recent infection. Two sets of blood cultures, sputum culture, and urinalysis with urine culture are ordered, and the patient is admitted to the ICU for possible acute stroke. Urinalysis and subsequent urine culture show cloudy urine, 5–10 white blood cells per high-power field, and 10^5 or greater extended-spectrum β-lactamase *E. coli*. The physician asks for your treatment recommendation. Which one of the following is best to recommend for this patient regarding his urinalysis and urine culture?

    A. Initiate treatment with ertapenem.
    B. Remove the urethral catheter and initiate treatment with ertapenem.
    C. Remove or exchange the urethral catheter and repeat urine studies.
    D. Limit treatment to 5–7 days.

52. An 80-year-old woman who lives in a nursing home presents to the ICU with urosepsis. Her medical history includes diabetes mellitus, hypertension, atrial fibrillation, and prior stroke. She has no allergies, and her home drugs include lisinopril, amlodipine, metoprolol, and warfarin. Which one of the following is best to recommend as empiric treatment for this patient?

    A. Ceftriaxone
    B. Ertapenem
    C. Piperacillin/tazobactam
    D. Moxifloxacin

53. A 24-year-old non-pregnant woman is admitted to the ICU with complaints of fever, rigors, pain on urination, and flank pain. She has no relevant medical history. On examination, the patient has a temperature of 104°F (40°C), blood pressure 80/40 mm Hg, heart rate 125 beats/minute, and respiratory rate 24 breaths/minute. Having received 3 L of intravenous fluids, she is initiated on a continuous infusion of norepinephrine. Local fluoroquinolone susceptibility rates are 88%. Which one of the following is the best empiric treatment recommendation for this patient?

    A. Oral ciprofloxacin
    B. Fosfomycin
    C. Intravenous levofloxacin
    D. Ceftriaxone

Questions 54–56 pertain to the following case.

T.V. is a 20-year-old female college student who is brought to the ED by her roommate. On examination, T.V. has a fever, altered mental status, and nuchal rigidity. During the examination, she develops seizure-like activity. She has no relevant medical history and takes no medications.

54. Which one of the following is the best next step for T.V.?

    A. CT scan of the head
    B. LP
    C. Dexamethasone intravenously 0.15 mg/kg
    D. MRI

55. T.V.'s LP reveals the following: elevated opening pressure, WBC 5 x 10^3 cells/mm^3 with 90% neutrophils, protein 250 mg/dL, and glucose 20 mg/dL. Which one of the following, in addition to vancomycin, is the best empiric treatment to recommend for T.V.?

    A. Ceftriaxone plus ampicillin
    B. Cefepime
    C. Ceftriaxone
    D. Meropenem

56. Which one of the following is the best adjunctive therapy to recommend for T.V.?

    A. Dexamethasone administered before or with antibiotics
    B. Rifampin in addition to other empiric antimicrobials
    C. Targeted temperature management
    D. Repeat LP

57. A 42-year-old man is admitted directly to ICU from an outside hospital with acute-onset altered mental status, fever, and rash. His medical history is significant for hypertension, diabetes mellitus, and chronic alcohol abuse. Results of head CT are unremarkable. An LP is performed, and the results are suggestive of bacterial meningitis. Which one of the following, in addition to vancomycin, is best to recommend for this patient?

    A. Ceftriaxone
    B. Ceftriaxone plus rifampin
    C. Ceftriaxone plus ampicillin
    D. Cefepime

Questions 58 and 59 pertain to the following case.

Z.R. is a 68-year-old woman admitted to the ICU from home with complaints of severe abdominal pain, nausea, and vomiting. On examination, she is febrile, hypotensive, and tachycardic and has significant abdominal rigidity and rebound tenderness.

58. Which one of the following is best to recommend first for Z.R.?

    A. CT scan with oral and intravenous contrast
    B. Abdominal ultrasonography
    C. Endoscopic retrograde cholangiopancreatography
    D. Surgical evaluation

59. On evaluation, Z.R. has diffuse peritonitis secondary to a ruptured colon. She is emergently taken to the operating room for a partial colectomy. Local susceptibility rates for fluoroquinolones are 92%. Which one of the following is best to recommend for Z.R.?

    A. Meropenem
    B. Tigecycline
    C. Cefepime
    D. Ciprofloxacin

60. A 58-year-old woman with respiratory failure and septic shock caused by acute pancreatitis is admitted to the ICU from an outside hospital. She requires mechanical ventilation and a continuous infusion of norepinephrine. An emergency CT scan of the abdomen reveals severe pancreatitis with about 40% necrosis and a focal collection of fluid. A CT-guided drainage of the fluid is performed and sent for evaluation. Which one of the following is best to recommend for empiric antimicrobial therapy in this patient?

    A. Piperacillin/tazobactam
    B. Meropenem
    C. Metronidazole
    D. No antimicrobial therapy indicated

Learner Chapter Evaluation: Other Common Infections in the ICU.

As you take the posttest for this chapter, also evaluate the material's quality and usefulness, as well as the achievement of learning objectives. Rate each item using this 5-point scale:

- Strongly agree
- Agree
- Neutral
- Disagree
- Strongly disagree

36. The content of the chapter met my educational needs.
37. The content of the chapter satisfied my expectations.
38. The author presented the chapter content effectively.
39. The content of the chapter was relevant to my practice and presented at the appropriate depth and scope.
40. The content of the chapter was objective and balanced.
41. The content of the chapter is free of bias, promotion, or advertisement of commercial products.
42. The content of the chapter was useful to me.
43. The teaching and learning methods used in the chapter were effective.
44. The active learning methods used in the chapter were effective.
45. The learning assessment activities used in the chapter were effective.
46. The chapter was effective overall.

Use the 5-point scale to indicate whether this chapter prepared you to accomplish the following learning objectives:

47. Design pharmacotherapy for catheter-associated bloodstream infections in the ICU based on patient characteristics, epidemiology, clinical presentation, and guideline-based recommendations.
48. Design pharmacotherapy for urinary tract infections in the ICU based on patient characteristics, epidemiology, clinical presentation, and evidence-based recommendations.
49. Design pharmacotherapy for intra-abdominal infections in the ICU based on patient characteristics, epidemiology, clinical presentation, and evidence-based recommendations.
50. Design pharmacotherapy for skin and soft tissue infections in the ICU based on patient characteristics, epidemiology, clinical presentation, and evidence-based recommendations.
51. Design pharmacotherapy for community-acquired pneumonia requiring ICU admission based on patient characteristics, epidemiology, clinical presentation, and evidence-based recommendations.
52. Design pharmacotherapy for CNS infections in the ICU based on patient characteristics, epidemiology, clinical presentation, and evidence-based recommendations.
53. Please provide any specific comments related to any perceptions of bias, promotion, or advertisement of commercial products.
54. Please expand on any of your above responses, and/or provide any additional comments regarding this chapter:

Questions 55–57 apply to the entire learning module.

55. How long did it take you to read the instructional materials in this module?
56. How long did it take you to read and answer the assessment questions in this module?
57. Please provide any additional comments you may have regarding this module:

Infection Critical Care II

Infection Critical Care II Panel

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Sepsis

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Reviewed by Liz G. Ramos, Pharm.D., BCPS; and Jodi A. Dreiling, Pharm.D., BCPS

LEARNING OBJECTIVES

1. Evaluate a patient for suspected sepsis, severe sepsis, or septic shock, identifying potential infection sites and using proper source control.
2. Distinguish pharmacokinetic and pharmacodynamic changes in the patient with sepsis to optimize antimicrobial treatment.
3. Design appropriate empiric antimicrobial therapy, including combination antimicrobial therapy when justified, in the patient with sepsis.
4. Justify de-escalation of antimicrobial therapy using patient and culture data.
5. Apply sepsis bundles to facilitate early antimicrobial therapy and demonstrate good antimicrobial stewardship.

ABBREVIATIONS IN THIS CHAPTER

MRSA	Methicillin-resistant *Staphylococcus aureus*
PCT	Procalcitonin
SIRS	Systemic inflammatory response syndrome
SSC	Surviving Sepsis Campaign
Vd	Volume of distribution

INTRODUCTION

Sepsis is a complex clinical syndrome that has been described since the age of Hippocrates. It may be simply described as the host's response to an infecting microorganism. The pathophysiology of this response is still being elucidated today, but it is known to involve several key pathways: innate and adaptive immunity, inflammation, coagulation, oxygenation, and endocrine. When the host's response to infection is inadequate, the result is extensive tissue injury and organ dysfunction. Management of sepsis targets its intricate pathogenesis. Goals of therapy include cardiorespiratory resuscitation, infection control, endocrine sufficiency, and immunomodulation. This chapter focuses on infection control through appropriate assessment and antimicrobial management of sepsis.

Epidemiology of Sepsis

Despite recent advances in the diagnosis and treatment of sepsis, it remains a major cause of morbidity and mortality. Sepsis is the 11th leading cause of death in the United States and the 10th leading cause of death among patients 65 years and older. Sepsis occurs most commonly in critically ill patients and is the fourth most common primary diagnosis of ICU admissions. According to CDC data from 2008, hospitalized patients with sepsis were 8 times more likely to die than were patients with other diagnoses, accounting for 17% of in-hospital deaths (Hall 2011).

Epidemiologic data spanning the past 3 decades have shown certain trends. According to hospital administration data, the prevalence of hospitalization owing to sepsis has increased, whereas the in-hospital mortality from sepsis has decreased. Results from a recent

study showed that the average increase in hospitalization for severe sepsis was 17.8% annually in 2003–2007. Specifically, 415,280 cases of severe sepsis were identified in 2003 compared with 711,736 cases in 2007 (a 71% overall increase) (Lagu 2012). The increased prevalence is likely influenced by increased recognition and changes in hospital coding preferences. Of interest, the increase in prevalence is greatest in adults 65 years and older, and the severity of all cases is increasing. The increased severity is shown by a decrease in hospitalization for severe sepsis with only one organ failure and an increase in hospitalization for severe sepsis with three or more organ failures (Lagu 2012; Kumar 2011).

Nonetheless, hospital mortality from sepsis has decreased over the years, with one study reporting an in-hospital mortality rate of 27.3% in 2007 compared with 39.6% in 2000. As fewer patients with sepsis are dying in the hospital, more patients are being discharged to other health care facilities (e.g., long-term care, skilled nursing facilities, rehabilitation) (Kumar 2011). The mortality rate of patients with sepsis discharged to other health care facilities is unknown. As the U.S. population continues to age and develop more comorbidities, sepsis will continue to be a common inpatient syndrome.

Definitions and Diagnostic Criteria for Sepsis

Sepsis portrays a continuum of severity classified as sepsis, severe sepsis, and septic shock. The terms *infection*, *bacteremia*, *septicemia*, *sepsis*, *sepsis syndrome*, and *septic shock* were used interchangeably until 1991, when Roger Bone proposed that the medical community condense and standardize sepsis terminology. Soon thereafter, the American College of Chest Physicians (ACCP) and the Society of Critical Care Medicine (SCCM) held a conference to discuss adopting standard definitions of sepsis, severe sepsis, and septic shock. The consensus statement published after the conference aimed to improve early bedside detection of sepsis, facilitate early therapeutic intervention, and standardize clinical research.

Sepsis was defined as the systemic response to infection; *severe sepsis* was sepsis associated with organ dysfunction, hypoperfusion abnormality, or sepsis-induced hypotension; and *septic shock* was sepsis-induced hypotension, persisting despite adequate fluid resuscitation, together with the presence of hypoperfusion abnormalities or organ dysfunction. *Sepsis-induced hypotension* was defined as a systolic blood pressure of less than 90 mm Hg or its reduction by at least 40 mm Hg (in the absence of other etiologies for hypotension) from baseline (Bone 1992). A blood lactate concentration of 4 mmol/L or higher is also considered sepsis-induced hypotension.

The authors also coined the term *systemic inflammatory response syndrome* (SIRS) to describe an inflammatory process seen in both infectious and noninfectious processes. As first used to define the systemic response to infection, SIRS includes specific abnormalities in four variables – temperature, heart rate, respiratory rate, and WBC. It was determined that patients had to have abnormalities in at least two of those variables to have sepsis. Randomized controlled trials of sepsis commonly use SIRS for study inclusion. A literature search found that 69% of clinical trials published in 1993–2001 used the 1991 ACCP/SCCM consensus conference standardized criteria for patient enrollment (Trzeciak 2005). Clinical trials published before the conference were more likely to require positive blood cultures and less likely to incorporate signs of organ dysfunction.

Incorporating the standardized definitions into clinical practice was not as immediate. A prospective international survey that interviewed 1058 physicians taking care of critically ill patients found that only 13% defined sepsis according to the 1991 ACCP/SCCM consensus statement (Poeze 2004). One reason for this variation is hesitation to embrace the SIRS criteria into the definition of sepsis. The four SIRS criteria are not exclusive to infectious processes, nor do they discern sepsis from other infections. In addition, because about one-half of all sepsis cases are culture negative, a diagnosis of sepsis relies more heavily on a list of nonspecific symptoms than on the underlying infection (Phua 2013; Martin 2003).

The definitions' increased use in clinical research and poor incorporation into clinical practice proved the need for revised guidance. A second international conference in 2001

BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:

- Pathophysiology of sepsis and septic shock
- Components of early goal-directed therapy and hemodynamic monitoring goals in sepsis
- Pharmacology, pharmacokinetics, pharmacodynamics, and spectrum of activity of antimicrobial agents

ADDITIONAL READINGS

The following free resources are available for readers wishing additional background information on this topic.

- Society of Critical Care Medicine and European Society of Intensive Care Medicine. Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: 2012 [homepage on the Internet].
- Roberts JA, Abdul-Aziz MH, Lipman J, et al. Individualized antibiotic dosing for patients who are critically ill: challenges and potential solutions. Lancet Infect Dis 2014;14:498-509.

resulted in an updated publication that kept the original definitions and broadened the criteria for the systemic response to infection. The new definition includes the original SIRS criteria together with other variables such as inflammation, hemodynamics, organ dysfunction, and tissue perfusion. Now, a diagnosis of sepsis is based on evidence of infection (documented or suspected) and "some of the following [variables]" (Levy 2003). The number of variables needed to diagnose sepsis was intentionally omitted to reflect clinical reality at the bedside.

With new understanding of the pathophysiology, certain biomarkers (e.g., plasma C-reactive protein and plasma procalcitonin) related to sepsis were added with the goal of increasing diagnostic sensitivity. Signs of early organ dysfunction were added because these may be the first indicators observed by clinicians (Levy 2003). The most recent criteria, published in the 2013 international guidelines, contain only minor changes (Dellinger 2013). Box 1-1 lists clinical variables considered in diagnosis.

The intent of the changes was to make the definition sufficiently specific to be a clinical aid at the bedside (Levy 2003). The authors emphasized that the variables should only be used to diagnose sepsis if they cannot be easily explained by other causes. The expanded criteria include variables needed to define severe sepsis. Overall, it may allow clinicians to use more data from physical examinations and professional experience, but it is argued that the expanded criteria make the definition of sepsis even less specific. Indeed, an observational study of ICU patients determined that the 1991 and 2001 criteria had sensitivities and specificities of 94.6% and 96.9% and 61.0% and 58.3%, respectively, compared with clinical judgment. The ability of the two definitions to correctly classify sepsis varied by patient time in the ICU; the 2001 definition had decreased diagnostic performance within the first 24 hours (Zhao 2012). When patients first arrive in the ICU, it is quicker to evaluate patients and make clinical decisions using the 1991 definition than using the lengthy 2001 definition. In addition, it is more difficult to commit the 2001 definition to memory, and not all of the laboratory values listed in the definition are widely available.

The 2001 definition has been recommended by international guidelines since 2008, but it is unclear whether its use has increased in clinical practice. Depending on the type of unit and the monitoring parameters that are routinely used, specific variables in the 2001 definition have been added to clinical decision-making. However, the principal signs continue to be the SIRS criteria.

Issues with heavy reliance on SIRS criteria to define sepsis continue to be examined. Not only is SIRS nonspecific for infection, but a retrospective study looking at a multicenter ICU database found that 1 in 8 patients with severe sepsis did not meet the minimum requirement of two SIRS criteria. These identified patients with SIRS-negative sepsis had a mortality trend similar to that of patients who met at least two SIRS criteria (Kaukonen 2015). There was also a linear increase in in-hospital mortality with each additional SIRS criteria that a patient met, suggesting that a requirement of two criteria to define sepsis is needed.

Given all this, the requirements for severe sepsis (SIRS or other clinical variables, known or suspected infection, and evidence of organ dysfunction) should be regarded equally with the understanding that not all patients will have all three requirements at a given time. Clinical judgment is key, and the definition of sepsis will continue to develop as our understanding of the underlying pathophysiology improves. Box 1-2 describes the sepsis classifications based on the current guidelines.

Going forward, the definitions will continue to evolve. In 2010, a recently formed global entity, the Global Sepsis Alliance (GSA), held its first meeting in conjunction with the Merinoff Symposium. The Merinoff Symposium, created by the Feinstein Institute for Medical Research, is a series of symposiums aimed at analyzing a particular disease in a

Box 1-1. Clinical Variables for Sepsis Diagnosis

General:
- Temperature > 38.3°C or < 36°C
- Heart rate > 90 beats/minute
- Respiratory rate > 20 beats/minute
- Altered mental status
- Increased fluid balance (> 20 mL/kg over 24 hr)
- Elevated blood glucose > 140 mg/dL (in absence of diabetes)

Inflammatory:
- WBC > 12 x 10^3 cells/mm^3 or < 4 x 10^3 cells/mm^3 or > 10% immature neutrophils
- Elevated plasma C-reactive protein
- Elevated plasma procalcitonin

Hemodynamic:
- Hypotension (SBP < 90 mm Hg; MAP < 70 mm Hg; or SBP decrease > 40 mm Hg in adults or < 2 SD below normal for age)

Organ dysfunction:

Pulmonary abnormalities
- Hypoxemia (Pao_2/Fio_2 < 300)

Renal abnormalities
- Urine output < 0.5 mL/kg/hr for at least 2 hr despite adequate fluid resuscitation
- SCr increase > 0.5 mg/dL

Hematologic abnormalities
- Platelet count < 100,000/mm^3
- Plasma total bilirubin > 4 mg/dL

Coagulation abnormalities
- INR > 1.5
- aPTT > 60s

Other abnormalities
- Ileus

Tissue Perfusion:
- Plasma lactate > 1 mmol/L
- Decrease capillary refill or mottling

Box 1-2. Sepsis Classifications Based on Current Guidelines

Sepsis: The presence (probable or documented) of infection plus systemic manifestations of infection (general variables and inflammatory variables)

Severe Sepsis: Sepsis plus evidence of sepsis-induced organ dysfunction or tissue hypoperfusion (organ dysfunction variables, hemodynamic variables, and tissue perfusion variables)

Septic Shock: Severe sepsis plus sepsis-induced hypotension despite adequate fluid resuscitation

global context, and one of the 2010 topics was sepsis. The GSA updated the definition of sepsis to be "a life-threatening condition that arises when the body's response to an infection injures its own tissues and organs" (Czura 2011). This implies that the criteria for sepsis are not met until there is evidence of tissue or organ damage.

Clinician evaluation of sepsis and severe sepsis is also becoming more difficult to differentiate. A recent ED study examining agreement between ED physician diagnosis and the 1991 and 2001 consensus sepsis definitions showed that of the physician-diagnosed sepsis cases, 71.4% and 67.9% would be re-diagnosed as severe sepsis according to the 1991 and 2001 definitions, respectively (Brown 2015). This continues to highlight deficient clinical application of the 1991 and 2001 consensus definitions. It also reveals a possible barrier to early identification. The goal should be to identify sepsis in its earliest stage, before organ dysfunction, to optimize patient outcomes.

Surviving Sepsis Campaign

To combat the international burden that sepsis had placed on health care systems, clinicians, and patients, the European Society of Intensive Care Medicine, SCCM, and the International Sepsis Forum created the Surviving Sepsis Campaign (SSC). The declared primary goal of SSC was to reduce sepsis mortality by 25% by 2009 through a 7-point agenda that would be rolled out in phases. Phase I was to develop awareness of the scope of the problem: the SSC was announced at several major critical care medicine conferences, starting with the Barcelona Declaration in 2002. In the declaration, a 5-point action plan for health care providers recognized targets for intervention: diagnosis, treatment, referral, education, and counseling. Phase II focused on developing and publishing guidelines: the SSC joined members from 11 international societies with interest and expertise in sepsis to create the first comprehensive, evidence-based management guidelines in 2004. The current, third edition includes updates based on data through fall 2012 and is supported by 30 organizations (Dellinger 2013).

INITIAL ASSESSMENT

Patient Identification

Early Identification

Early identification of the patient with sepsis is paramount in helping to improve mortality and morbidity. In fact, delay in the identification of sepsis and, therefore, delay in the appropriate antimicrobial treatment of sepsis, is associated with an overall increase in organ failure and mortality. Any health care discipline that is knowledgeable about sepsis can be valuable in the early identification of sepsis. Ideally, the process should start as soon as the patient enters the hospital, either in the ED or in the general ward.

The SSC recommends routine screening for sepsis in patients with suspected infections. Because the clinical features of sepsis are variable, practitioners should try to evaluate all patients with possible or suspected sepsis by evaluating for clinical or physiologic derangements consistent with sepsis. The newest SSC diagnostic criteria for sepsis include general vital sign derangement and then inflammatory, hemodynamic, organ dysfunction, and tissue perfusion variables (Dellinger 2013). These clinical and physiologic features can be used to help the practitioner identify possible patients with sepsis as early as possible.

Sepsis screening tools can be used to help with the early identification of patients with sepsis. One particular tool used a three-step sepsis identification system to help early identification of patients. This tool had a high sensitivity (96.5%) and specificity (96.7%). The use of this tool decreased sepsis-related mortality by 11.8% (Moore 2009). Clinical decision support systems integrated within the electronic health system may also be used in the early identification of patients with possible sepsis (Amland 2014).

Identification of Source

Obtaining Cultures

After identifying patients with sepsis, the health care provider should evaluate for all possible sources of infection. Historically, the most common sites of severe sepsis in the United States are respiratory infections (about 40%), bloodstream infections (about 20%), genitourinary infections (about 10%), and abdominal infections (about 9%) (Mayr 2014).

Health care practitioners who suspect sepsis because of clinical findings should obtain at least two blood cultures (both aerobic and anaerobic bottles) before initiating antimicrobials, given the occurrence of rapid sterilization of the blood (Figure 1-1). However, obtaining cultures should not delay prompt antimicrobial treatment for suspected sepsis. At least one peripheral blood culture should be obtained, and blood through any vascular access should be cultured (unless inserted less than 24 hours prior). Other possible infection sites should be cultured, such as respiratory, urine, CSF, wounds, or body fluids. Respiratory samples can be

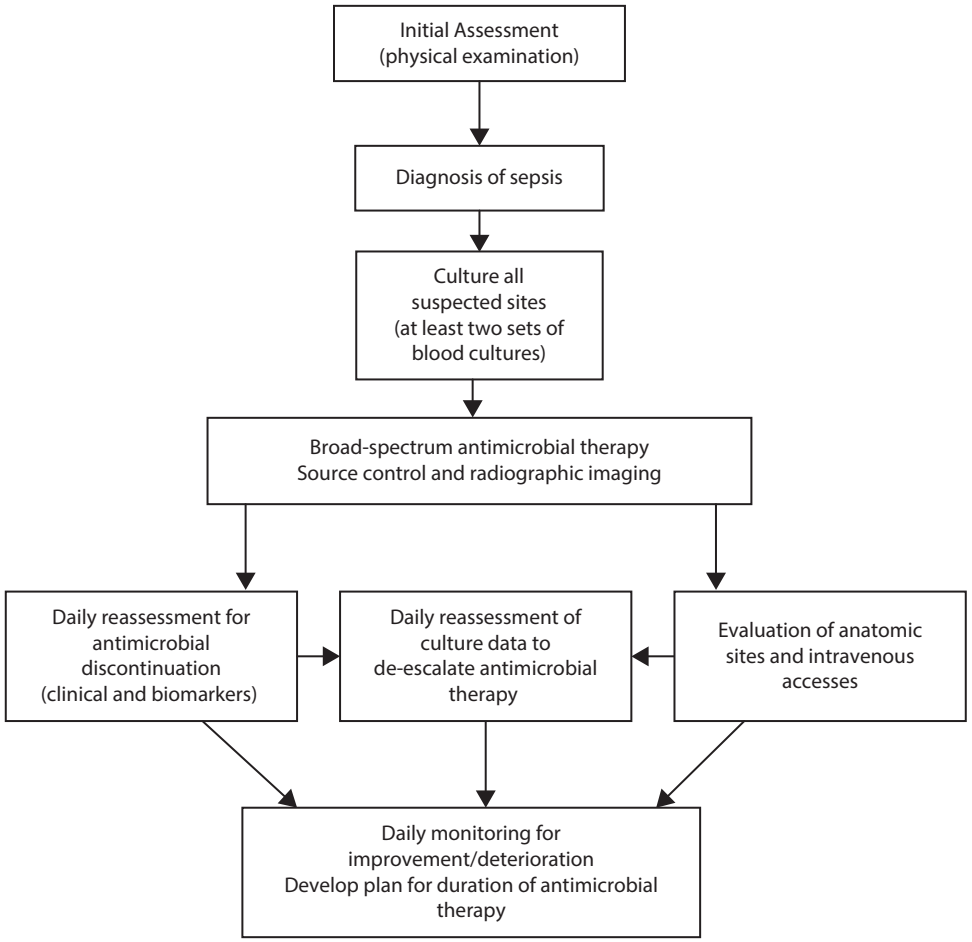

Figure 1-1. General approach to the initial management of suspected sepsis.

expectorated sputum, induced sputum, or bronchoscopic alveolar lavage. These samples should be sent for any possible microbial organisms, including viruses (e.g., seasonal influenza, respiratory syncytial virus, cytomegalovirus, herpes) if clinically indicated and any other microbial organisms given the patient's medical history and presentation (e.g., *Pneumocystis jiroveci*, fungal, mycobacterial, *Nocardia* spp., *Legionella* spp., *Histoplasma capsulatum*). Urine should be sent for analysis, which includes direct microscopic visualization, quantitative analysis, and culture. All cultures should be obtained within the first 3 hours of presentation (Dellinger 2013).

Source Control

The overall goal for source control is to identify possible infection sites and to eliminate the source when possible. Radiographic studies should be performed to help confirm diagnosis. These studies are also important to help determine whether the patient is a surgical candidate. Source control is a vital component of the early management of sepsis, especially in infections such as necrotizing fasciitis, ischemic bowel, toxic megacolon, severe *Clostridium difficile* infection, ascending cholangitis, infectious necrotizing pancreatitis, infectious empyema, obstructive uropathy, and complicated pyelonephritis. For these cases, prompt surgical intervention may be needed to appropriately eliminate the infectious process.

In addition, source control can be accomplished by the removal of any possible infected catheters or tunneled devices. The SSC recommends that interventions for source control be performed within 12 hours after the diagnosis is made, if feasible. They also recommend that intravascular devices that are suspected sources of infection be removed after adequate vascular access has been obtained, preferably at a site different from where the suspected infected intravascular device was placed (Dellinger 2013).

ANTIMICROBIAL PHARMACOKINETIC AND PHARMACODYNAMIC CHANGES IN SEPSIS

Pharmacokinetics of Antimicrobials

Pathophysiologic changes in sepsis significantly influence antimicrobial pharmacokinetics and pharmacodynamics. These pharmacokinetic alterations may affect the ability to obtain adequate concentrations at the infection site and may negatively affect clinical outcomes. Proper dosing of antimicrobials is essential in the critically ill population to achieve adequate antimicrobial concentrations for individual patients while minimizing and preventing adverse effects. However, antimicrobial dosing is a challenge in the sepsis population because of the lack of pharmacokinetic-pharmacodynamic data; therefore, most clinicians use recommended doses according to clinical data (adjusted for hepatic/renal insufficiency), small case reports, and expert opinion. In fact, recent data suggest that empiric recommended antimicrobial dosing does not achieve adequate concentrations, and the use of standard dosing is associated with increased risk of subtherapeutic concentrations in 19% of patients (De Waele 2014). A clear understanding of pharmacokinetic changes in sepsis is important in effectively designing antimicrobial regimens that can optimize pharmacodynamic parameters and source concentrations.

The ultimate goal of antimicrobial therapy is to achieve adequate concentrations at the infection site. Volume of distribution (Vd) and clearance play a significant role in the ability to achieve this goal. In general, initial serum antimicrobial concentrations can be explained by Cmax = loading dose/Vd. Given this formula, it is easy to see how the increase in volume can negatively influence concentrations.

Distribution

Antimicrobial Vd is altered in sepsis by several different mechanisms. The inflammatory effects of sepsis increase vascular permeability and vasodilation. Fluid from the intravascular space leaks into the interstitial space, causing a third-space phenomenon. This change and redistribution of fluid increases the Vd of hydrophilic antimicrobials (Figure 1-2).

Volume is further affected by aggressive fluid resuscitation in the early stages of severe sepsis and septic shock, when most crystalloids administered will reside in the interstitial space hours after administration. The increase in volume during the resuscitative period may lead to subtherapeutic antimicrobial concentrations and place the patient at risk of treatment failure, increased antimicrobial resistance, or both.

Hydrophilic antimicrobials may need larger doses and/or loading doses to achieve adequate concentrations at the infection site. Lipophilic antimicrobials are less influenced by changes in volume because of their wide distribution in adipose tissues and intracellular compartments. Tissue perfusion may also affect the ability to achieve proper tissue concentrations. In sepsis, local tissue perfusion is commonly compromised. This decrease in tissue perfusion may diminish the tissue concentrations of hydrophilic antimicrobials, leading to subtherapeutic concentrations at the infection site.

Clearance

Alterations in antimicrobial clearance depend on the metabolic and elimination pathways of the drugs. Progression of renal dysfunction and decreases in glomerular filtration will decrease the clearance of antimicrobials that are eliminated by the kidney. However, in preserved kidney function, renal clearance may actually be increased or augmented because

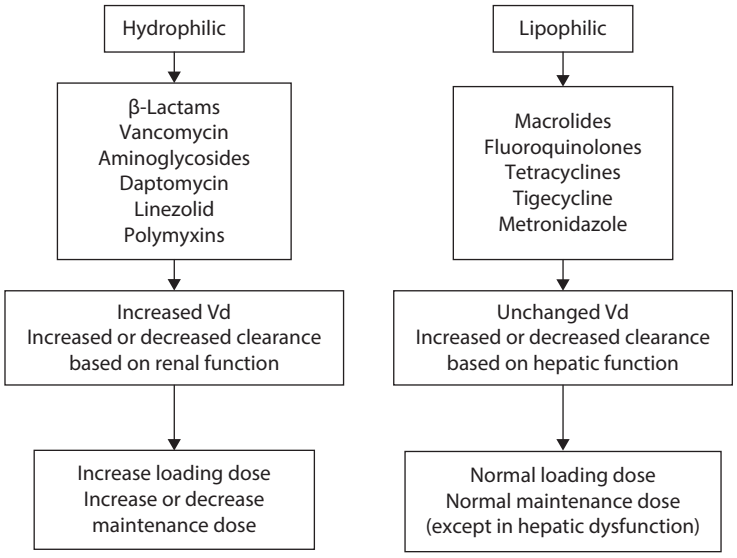

Figure 1-2. Summary of pharmacokinetic changes in antimicrobials.

of the increase in perfusion to the kidney seen in high output states like sepsis. It is important for the clinician to recognize the possibility of augmented renal clearance to prevent the underdosing of antimicrobials (Udy 2010).

The impact of hepatic dysfunction on the clearance of antimicrobials is less clear. Hepatic function is dependent on liver perfusion, free fraction of the antimicrobial, and intrinsic clearance of the antimicrobial in the liver by metabolic pathways. Agents can be categorized as high- or low-extraction drugs. High-extraction drugs are influenced mainly by the perfusion of the liver. For high-extraction drugs, the clearance is best described as CL = QH, where CL is clearance and QH is liver flow rate. According to this principle, changes in perfusion will lead to changes in hepatic clearance. In sepsis, there may be a high cardiac output state and an increase in perfusion to liver, leading to increased clearance of high-extraction drugs by the liver. However, there also can be a decrease in perfusion in sepsis, leading to decreased clearance of high-extraction drugs. For low-extraction drugs (i.e., clindamycin and metronidazole), the clearance is best described as CL = (f_u) (CLint), where f_u is the free drug fraction and CLint is the intrinsic clearance of the drug. In sepsis, hepatocellular enzyme activity may also be decreased, leading to the decreased clearance of antimicrobials that are metabolized by hepatocellular enzymes.

Protein Binding

Protein binding is significantly influenced in sepsis. Albumin and α_1-acid glycoprotein are the predominant proteins that bind medications. Albumin and total protein concentrations are decreased in the critically ill patient because of a decrease in production of proteins, an increase in volume, capillary permeability, and catabolism. Hypoalbuminemia is another cause of increased Vd for antimicrobials that are highly protein bound (greater than 70%; ceftriaxone, clindamycin, daptomycin, ertapenem, tigecycline) and moderately protein bound (30%–70%; azithromycin, ciprofloxacin, linezolid, piperacillin, vancomycin, voriconazole). In fact, small changes in albumin can significantly increase unbound drug, which is then free to distribute to the tissues (Ulldemolins 2011).

α_1-Acid glycoprotein (AAG), an acute-phase protein, is generally increased in the sepsis population. Agents that bind to AAG may have less free drug available, resulting in decreased concentrations at the infection site. However, few antimicrobials are bound to AAG (macrolides, clindamycin; low to moderate binding). Protein binding also influences antimicrobial clearance. The kidneys and liver eliminate free, unbound drug. In hypoalbuminemia, any drug that is highly protein bound will have higher free drug concentrations available to the kidney or liver for elimination in intact organ function. See Figure 1-2 for a summary of the ways in which sepsis influences pharmacokinetic and dosing.

Pharmacodynamic Properties

Antimicrobial pharmacodynamics is the relationship of drug concentration in the blood or at the infection site to the overall killing of the microorganism. Pharmacodynamic principles can be helpful in designing and optimizing antimicrobial regimens. In general, there are three classifications of pharmacodynamic parameters: (1) time-dependent killing, (2) concentration-dependent killing, and (3) combination of time- and concentration-dependent killing. Simply stated, with time-dependent antimicrobials, microorganism killing is optimized when the unbound concentration of the antimicrobial is above the MIC at the infection site for most of the dosing interval (T > MIC). The overall goal is to maximize the duration of exposure, whereas with concentration-dependent antimicrobials, microorganism killing is optimized as the maximum concentration (Cmax) at the infection site increases above the MIC (Cmax/MIC). The goal with these antimicrobials is to maximize the concentration while avoiding adverse effects.

The concentration-dependent antimicrobials generally have some degree of post-antibiotic effect, or persistent killing of the microbe for a period when the concentrations fall below the MIC. The third group has properties of both time- and concentration-dependent killing. These antimicrobials, which also tend to have a post-antibiotic effect, are best described using the AUC/MIC (Connors 2011). Table 1-1 summarizes the pharmacodynamic properties of common antimicrobials.

Hydrophilic Antimicrobials

Penicillins, Cephalosporins, Carbapenems

β-Lactam antimicrobials are among the agents most commonly used in patients with sepsis (Table 1-2). Penicillin, cephalosporins, cephalosporin, and carbapenem antimicrobials share time-dependent pharmacodynamic properties. Because of this principle, the optimal pharmacodynamic parameter for β-lactam antimicrobials is the percent of free drug plasma concentration above the MIC (% *f*T > MIC). Studies have shown that *f*T > MIC of at least 50% is essential for adequate bactericidal effect with β-lactam antimicrobials, although some newer research suggests that 100% *f*T > MIC is needed for cefepime or ceftazidime (McKinnon 2008). Other authors have found worse outcomes with less than 50% *f*T > MIC and improved outcomes with 50%–100% *f*T > MIC in patients receiving β-lactams (Roberts 2014a,b). Therefore, designing antimicrobial regimens to target at least 50% *f*T > MIC seems reasonable.

Few studies have evaluated the pharmacokinetics-pharmacodynamics of carbapenems in the sepsis population. Some study investigators evaluated meropenem in 14 critically ill patients with sepsis using two dosing regimens based on renal function: 1 g three times daily (CrCl greater than 50 mL/minute/1.73 m^2) and 1 g twice daily (CrCl less than 50 mL/minute/1.73 m^2). They showed that with both regimens,

Table 1-1. Pharmacodynamic Properties of Antimicrobials

Antimicrobial	Pharmacodynamic Property			Goals for Optimization of Therapy
	Time-Dependent (T>MIC)	Concentration-Dependent (Cmax/MIC)	Both Properties (AUC/MIC)	
Hydrophilic				
Penicillins	✓			≥ 50% *f*T > MIC
Cephalosporins	✓			≥ 50%–70% *f*T > MIC
Carbapenems	✓			≥ 30%–40% *f*T > MIC
Aminoglycosides		✓		*f*Cmax/MIC ≥ 10
Vancomycin			✓	> 400 AUC_{0-24}/MIC
Linezolid			✓	AUC_{0-24}/MIC
Polymyxins			✓	AUC_{0-24}/MIC
Daptomycin		✓		*f*Cmax>MIC
Lipophilic				
Fluoroquinolones			✓	100–125 AUC/MIC[a] 30–50 AUC/MIC[b]
Macrolides			✓	AUC_{0-24}/MIC
Tigecycline			✓	AUC_{0-24}/MIC
Metronidazole		✓		Not well defined
Tetracyclines			✓	AUC_{0-24}/MIC

[a]Gram-negative organisms.

[b]Gram-positive organisms.

Information from: Conners KP, Kuti JL, Nicolau DP. Optimizing antibiotic pharmacodynamics for clinical practice. Pharmaceut Anal Acta 2013;4:1-8; and Martinez MN, Papich MG, Drusano GL. Dosing regimen matters: the importance of early intervention and rapid attainment of the pharmacokinetic/pharmacodynamic target. Antimicrob Agents Chemother 2012;56:2795-805.

meropenem concentrations were adequate (greater than 50% T > MIC) for all patients. Doripenem pharmacokinetics-pharmacodynamics were evaluated in critically ill patients with nosocomial pneumonia. In 31 patients, doripenem clearance and Vd were significantly larger than previously reported in healthy patients. Given these findings, the authors suggest that regular intermittent dosing (500 mg every 8 hours) will not achieve adequate concentrations if the patient weighs more than 100 kg and the MIC of the organism is greater than 4 mg/L (Roberts 2013).

Extended/prolonged infusion (i.e., over more than 4 hours) or continuous infusion of β-lactam antimicrobials may be used to optimize the pharmacodynamic goals. One study showed that continuous infusion piperacillin optimized *f*T > MIC, compared with standard therapy (Roberts 2010). Extended-infusion cefepime decreased mortality (from 20% to 3%; p=0.03) in patients with *Pseudomonas aeruginosa* bacteremia, pneumonia, or both, compared with standard therapy (Bauer 2013). Randomized, well-designed trials are needed to evaluate extended or continuous infusions before they are applied to the entire critical care population. However, these methods of administration can be used on a case-by-case basis to improve pharmacodynamic end points and possibly clinical outcomes, especially when treating multidrug-resistant organisms.

Aminoglycosides

Aminoglycosides remain popular treatments for sepsis because of their rapid antimicrobial effects and post-antibiotic effects. The aminoglycoside pharmacodynamics in the sepsis population are well described in the literature. In general, aminoglycosides in patients with sepsis have a significantly increased volume compared with that in patients without sepsis, resulting in decreased serum and tissue concentrations. In the sepsis population, because aminoglycoside clearance is directly related to renal function,

Table 1-2. Dosing Adjustments for Common Antimicrobials in Sepsis

	Suggested Goals and Dosing Adjustment	
Antimicrobial	Normal Renal Function	Moderate to Severe Renal Dysfunction
Penicillins Carbapenems Cephalosporins	Use extended (or continuous) infusion to optimize T > MIC; can also decrease dosing interval	Use loading dose on day 1 to optimize tissue concentrations. Increase dosing interval
Vancomycin	Use loading dose of 30 mg/kg/dose on day 1 to optimize tissue concentrations. Maintenance dose is generally 15 mg/kg. Dose to maintain goal trough concentrations of 15–20 mg/L	Use loading dose of 30 mg/kg/dose on day 1 to optimize tissue concentrations. Maintenance dose is generally 15 mg/kg. Dosing interval based on renal function and typically needs to be increased. Dose to maintain goal trough concentrations of 15–20 mg/L
Fluoroquinolones	Use larger doses to optimize Peak/MIC ratio; levofloxacin may require 500 mg every 12 hr in patients with high estimated GFR[a]; monitor for seizures	Increase dosing interval for levofloxacin or ciprofloxacin
Aminoglycosides	Optimize Peak/MIC ratio of ≥10; may need to use higher doses; trough concentrations should be < 1 mg/L	Optimize Peak/MIC ratio of ≥10; may need to increase dosing interval to greater than 24 hours; individualize dosing by using MIC data (if available)
Polymyxins	Colistin: Use 2.5 mg/kg of colistin base every 12 hr[b] Polymyxin B: 15,000–25,000 units/kg/day divided every 12 hr; use total body weight	Colistin: Use loading dose on day 1 to optimize tissue concentrations; dosing interval may need to be increased Polymyxin B: Use loading dose on day 1 to optimize tissue concentrations; no adjustment needed for renal impairment

GFR = glomerular filtration rate

[a]Pea F, Di Qual E, Cusenza A, et al. Pharmacokinetics and pharmacodynamics of intravenous levofloxacin in patients with early-onset ventilator pneumonia. Clin Pharmacokinet 2003;42:589-98.

[b]1 million units of colistimethate = 80 mg of colistimethate = 30 mg of colistin base activity.

Information adapted from: Roberts JA, Lipman J. Pharmacokinetic issues for antibiotics in the critically ill patient. Crit Care Med 2009;37:840-51.

aminoglycoside clearance can be significantly increased in hyperdynamic patients with preserved renal perfusion, or significantly decreased in patients with renal insufficiency.

The overall pharmacodynamic goal for aminoglycosides is a peak concentration of at least 10 times the MIC. Because of the hydrophilic properties of the aminoglycosides and low distribution, this pharmacodynamic goal may be difficult to achieve with standard doses, especially with gram-negative infections that have a high MIC. In a study that evaluated standard dosing of amikacin and gentamicin in the critically ill patient, 15 mg/kg or more of amikacin and 3 mg/kg or more of gentamicin were administered for initial doses on the basis of actual body weight. As a group, only 19% of the population achieved the targeted peak concentration. The targeted peak was achieved in 24% of the amikacin group and 4% of the gentamicin group (Roger 2015). Amikacin may require loading doses higher than 25 mg/kg to achieve the pharmacodynamic goal (Mahmoudi 2013), and tobramycin and gentamicin may need loading doses greater than 7 mg/kg.

Vancomycin

Similar to the aminoglycosides, vancomycin has been well studied in the critically ill and sepsis population. Vancomycin is a hydrophilic antimicrobial, but it has a larger Vd than the aminoglycoside antimicrobials. The kidney is responsible for most elimination (80%–90%), whereas the remainder is eliminated by biliary excretion. Tissue penetration depends on the degree of inflammation. For cerebrospinal infections, vancomycin concentrations in the CSF are 29%–48% of serum concentrations, compared with 0%–18% in uninflamed meninges. Lung penetration is highly variable, and concentrations may be as low as a ratio of 6:1 (serum/lung).

The vancomycin pharmacodynamic goal is an AUC/MIC ratio greater than 400. This goal may be difficult to attain with gram-positive organisms having an MIC greater than 1 mcg/mL. In one evaluation of vancomycin dose requirement in patients with SIRS, an increase in vancomycin clearance occurred as the number of SIRS criteria increased. Furthermore, AUC/MIC decreased significantly as the number

of SIRS criteria increased (Shimamoto 2013). Because of the volume changes in the patient with sepsis, a one-time loading dose (25–30 mg/kg; total body weight) should be administered to ensure that adequate concentrations are obtained within the first 24 hours. Some experts suggest limiting individual vancomycin doses to 2–3 g (Liu 2011; Rybak 2009).

Polymyxins

The use of polymyxin antimicrobials is increasing because of the increase in multidrug resistant, gram-negative organisms. Unfortunately, there is a paucity of pharmacokinetic data with this class of antimicrobials in the sepsis population. More so, pharmacodynamic parameters for colistin and polymyxin B in the critically ill patient are not well established. Some data suggest that the polymyxins have both concentration- and time-dependent killing, thus, the optimal pharmacodynamic goal may be the AUC/MIC. However, more studies are needed to confirm this goal.

Clinically, colistin is administered intravenously as an inactive prodrug, colistimethate sodium, which is then hydrolyzed into colistin (active drug) in vivo. Dosing of colistin can be confusing because the package insert lists colistin base activity; however, the literature uses colistimethate sodium. The conversions between the three are as follows: 1 million units of colistimethate sodium = 80 mg of colistimethate sodium = 30 mg of colistin base activity. Colistin tends to have poor distribution into tissues, especially lung parenchyma, pleura, and CSF, which may limit its efficacy in those infections (Imberti 2010). In healthy subjects, colistin's half-life is about 1.5–2 hours. At standard dosing (240 mg every 8 hours), colistin's half-life in critically ill patients can be prolonged up to 14 hours because of decreased renal elimination. Hence, colistin concentrations may be subtherapeutic until a steady-state concentration can be achieved. Therefore, loading doses should be used to optimize colistin concentrations early in therapy (Plachouras 2009).

Some investigators suggest using high-dose, extended-interval dosing given data from 28 critically ill patients. They used a loading dose of 270 mg of colistin base, followed by 130 mg of colistin base every 12 hours (CrCl greater than 50 mL/minute/1.73 m^2) and 130 mg every 24 hours (CrCl 20–50 mL/minute/1.73 m^2), or 130 mg every 48 hours (CrCl less than 20 mL/minute/1.73 m^2). With this dosing regimen, they showed a clinical cure rate of 82.1%; however, 17.8% of patients developed acute kidney injury (Dalfino 2012). For pulmonary infections, the ability to obtain adequate pulmonary concentrations of colistin is questionable with systemic therapy (Imberti 2010). Recent evidence suggests that adding inhaled colistin as an adjunct therapy to systemic colistin/polymyxin B improves microbiological outcomes (Valachis 2015; Michalopoulos 2008).

Some clinicians are moving away from colistin and using polymyxin B, for two reasons. Because polymyxin B is an active drug, it does not need to be converted in vivo. Furthermore, newer data suggest that polymyxin B is not appreciably cleared by the kidneys (urinary recovery of only 4%), and correlation of total body clearance of polymyxin B and CrCl is poor (r^2 = 0.008). According to these data, polymyxin B needs no adjustment for renal impairment, which simplifies its use clinically and may be able to provide better tissue concentrations than renal-adjusted colistin regimens. Polymyxin B should be dosed using total body weight (Sandri 2013). However, clinical efficacy data are lacking with polymyxin B in the critically ill patient. Regardless of the polymyxin agent chosen, the pharmacokinetics and pharmacodynamics must be evaluated to optimize therapy and prevent further resistance in these difficult-to-treat patients.

Lipophilic Antimicrobials

Fluoroquinolones

Fluoroquinolones are lipophilic antimicrobials that have excellent tissue penetration. Sepsis minimally influences the Vd for the fluoroquinolones. Fluoroquinolones have both concentration- and time-dependent killing. For gram-negative infections, the optimal pharmacodynamic goal is an AUC/MIC greater than 100–124. For gram-positive infections, the optimal pharmacodynamic goal is an AUC/MIC greater than 30–50. Ciprofloxacin may require larger doses or more frequent dosing in patients with normal renal function to achieve pharmacodynamic goals because of decreased maximum concentrations with fluid shifts (Szalek 2012). Normal intravenous doses of levofloxacin can achieve pharmacodynamic goals, but caution should be used for MICs greater than 2 (Benko 2007) or in patients with augmented renal function (Pea 2003).

EMPIRIC ANTIMICROBIAL THERAPY

Timing of Antimicrobial Therapy

Obtaining cultures and administering antimicrobial therapy are essential care elements of the 3-hour sepsis bundle. Obtaining clinically appropriate cultures before administering antimicrobials is crucial to increase the chances of identifying a causative organism and to ensure definitive therapy. The SSC guidelines recommend administering effective intravenous antimicrobials within 1 hour of recognition of severe sepsis or septic shock (Dellinger 2013). This recommendation is carried over from previous editions of the guidelines and is largely based on one landmark trial, which showed that with each 1-hour of delay in antimicrobial therapy, patients with septic shock had a 7.6% decrease in survival (Kumar 2006). More recent studies have confirmed that the mortality risk also applies to patients with severe sepsis. Analysis of patient data from the SSC international registry revealed a linear increase in the risk of mortality for each 1-hour delay in antimicrobial administration from hour 1 to hour 6 after suggestion of sepsis for patients with either severe sepsis or septic shock (Ferrer 2014). These findings show association,

not causation, because it would be unethical to perform prospective, controlled trials. However, there is adequate evidence from the many large, retrospective trials to show a mortality benefit in prompt antimicrobial administration. Eradicating the infection is just as important as reversing and preventing the destructive physiologic sequelae of sepsis for patient survival.

Timely administration of antimicrobials can be problematic. The guideline recommendation is considered a best practice, yet it is not the standard of care. In many of the trials examining time to antimicrobial administration from identification of sepsis, only 15%–30% of patients received therapy within 1 hour (Ferrer 2014; Gaieski 2010; Kumar 2006). However, most patients can receive antimicrobials within 3 hours (Ferrer 2014; Gaieski 2010). Setting a goal of antimicrobial administration that is consistent with the SSC 3-hour bundle is achievable and still confers survival benefit.

There are many barriers to prompt administration of antimicrobials. Patient identification is the first step, and misdiagnosis will delay initiation of life-saving therapies. Nonpharmacologic elements of the 3-hour bundle include obtaining blood for laboratory data, obtaining appropriate cultures, and administering fluids. Intravenous access is often an issue because patients arriving from the ED or wards may not have established intravenous access or may have only one line, and nurses are concomitantly administering fluids and other drugs (e.g., vasopressors). In the acute situation, without central intravenous access, all antimicrobials can be given through peripheral lines. If empiric therapy includes more than one antimicrobial, it is important to determine which drug should be administered first and whether coadministration is possible depending on product compatibility. Clinicians should be cognizant of the length of administration of the drug and consider the possibility of rapid infusion or bolus administration.

Even with protocols in place, the process can be chaotic, leading to delays in prescribers ordering or nurses hanging antimicrobials. Creating order sets in electronic physician order entry systems can decrease the chance that a critical order is missed. Marking the order as STAT will communicate urgency to the pharmacy verifying and filling the order. Pharmacists on the units can help coordinate efforts by expediting retrieval of the drugs from the pharmacy and communicating with health care teams and nurses about prompt ordering and administration. Storing a supply of premixed antimicrobials in automated dispensing cabinets on the units is recommended, keeping in mind drug stability (Dellinger 2013).

Appropriate Antimicrobial Therapy

Choosing an appropriate antimicrobial is as important as timely administration. As one retrospective, single-center study found, the survival benefit of administering antimicrobials within 1 hour of sepsis identification was greater if the antimicrobials were active in vitro against all causative organisms (Gaieski 2010). In patients with septic shock, inappropriate initial therapy resulted in a 5-fold decrease in survival to hospital discharge (Kumar 2009). Inappropriate therapy is based on microbiological confirmation of the causative organism and its antimicrobial sensitivities. It is defined as inappropriate when no agents used in initial therapy are active in vitro against the causative organism. Because most current microbiological identification techniques from cultures take at least 24 hours, initial antimicrobial therapy is empiric, and appropriate therapy is not guaranteed.

Designing Empiric Antimicrobial Therapy

Pharmacists play a key role in designing initial empiric antimicrobial therapy. The SSC guidelines and sepsis bundles identify pharmacists as integral members of the health care team who should be consulted for designing empiric antimicrobial therapy. Because early administration and appropriateness of therapy are crucial, the SSC guidelines recommend that initial empiric therapy consist of one or more drugs that have activity against all likely pathogens (Dellinger 2013). Bacteria make up most causative organisms of sepsis, followed by fungal and viral pathogens. Empiric antimicrobial therapy will always include antibiotics, and antifungals or antivirals should only be initiated if the patient presents with specific risk factors.

The prevalence of the two main classes of bacteria causing infections in patients with sepsis has varied over time. In the late 20th century, gram-negative bacteria made up most sepsis cases. Toward the turn of the 21st century, gram-positive bacteria rose as the main causative pathogen in sepsis cases. However, data show that since 2008, gram-negative organisms have once again become the predominant class. A U.S. hospital administration data set showed that gram-negative bacteria were the causative pathogen in 20.5% of severe sepsis cases, gram-positive bacteria accounted for 16.8% of the cases, and unknown organisms made up 61.6% of the cases (Ani 2015). Fungal organisms accounted for less than 1% of the cases, but their prevalence almost tripled during the 9-year period (Ani 2015). Data from studies examining inappropriate antimicrobial therapy report that 35%–50% of sepsis cultures grow gram-positive organisms, 25%–35% grow gram-negative organisms, and 3%–4% grow anaerobic organisms (Gaieski 2010; Kumar 2009).

Designing an empiric therapy begins with identifying the most likely infectious sources for the patient and knowing the most common causative pathogens for each source. The main sources of sepsis are respiratory, intra-abdominal, and urinary; these account for more than 60% of cases. Other sources include skin and soft tissue, surgical sites, CNS, intravascular catheters, bone, and renal.

For patients who are already receiving antimicrobial therapy before sepsis is identified, it is important to broaden coverage to include new sources of infection and consider the potential for resistance development to the current regimen. Recently used antimicrobials should be avoided,

and coverage of resistant organisms should be considered. Patient risk factors for resistant organisms include length of hospitalization before infection, inadequate treatment for a prior known infection, prior antimicrobial administration, hospitalization within the past 3 months, residence in a health care facility, and exposure to invasive devices. In addition, hospital antimicrobial resistance patterns should be considered. Most hospitals collect susceptibility data on bacterial isolates analyzed in their microbiology laboratory and report them regularly as an antibiogram. Every hospital should report methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus* spp. rates, and some may report extended-spectrum β-lactamase rates.

Other multidrug-resistant organisms seen in critically ill patients are *Acinetobacter baumannii*, *P. aeruginosa*, *Klebsiella pneumoniae*, *Enterobacter* spp., and *Stenotrophomonas maltophilia*. Patient-specific culture history, including the current admission and any recent admissions, which is generally available through electronic medical records, should be consulted. Patient-related variables should influence therapy decisions. Drug allergies or intolerances should be identified. Underlying diseases and immunosuppression that expose patients to specific organisms should be considered.

Antimicrobial therapy that covers both gram-positive and gram-negative organisms is mandatory in patients with severe sepsis or septic shock. Initial antimicrobial dosing should be aggressive, and pharmacokinetic and pharmacodynamic data should be used to optimize concentrations at the site of the infection. Using microbiological data from patients with sepsis, the most common gram-positive organisms are *Staphylococcus* spp. and *Streptococcus* spp. The most common gram-negative organisms are Enterobacteriaceae and *P. aeruginosa* (Ani 2015).

Because empiric therapy should cover all likely pathogens, an extended-spectrum penicillin with a β-lactamase inhibitor, a third- or fourth-generation cephalosporin, or an antipseudomonal carbapenem should be used. The choice of antimicrobial will depend on hospital formularies and antibiograms, as well as patient-related variables such as infection source and previous microbiological data. Vancomycin should be added if the patient is at risk of MRSA, penicillin-resistant pneumococcal strains, or ampicillin-resistant *Enterococcus* spp. Linezolid is an acceptable alternative to vancomycin for MRSA coverage in documented vancomycin failure or intolerance. However, linezolid should not be the first choice empirically because it is bacteriostatic and has limited efficacy data for serious infections. Aminoglycosides should not be used as monotherapy because of the decreased efficacy for gram-negative bacteremia and lack of gram-positive coverage. In addition, aminoglycosides have poor penetration into lungs, abscesses, and the CNS; therefore, they should not be used as empiric monotherapy if infections involving these sites are suspected. The glycylcycline called tigecycline should be avoided as initial therapy because it

Patient Care Scenario

A 45-year-old woman (height 64 inches, weight 63 kg) is admitted for severe acute respiratory distress syndrome and pneumonia. She has a medical history of uncontrolled hypertension and chronic kidney disease (baseline SCr 1.8 mg/dL). She was recently hospitalized for hypertensive emergency. In the ED, despite aggressive resuscitation, she required norepinephrine to maintain goal blood pressure. She was given one dose of ceftriaxone and azithromycin. Sputum and blood cultures were obtained, and she was transferred to the medical ICU for further treatment. In the MICU, she is mechanically ventilated, requiring an Fio_2 of 70% to maintain goal SaO_2. Pertinent laboratory values are SCr 2.5 mg/dL and lactate 5.7 mmol/L. The patient is anuric. What would be best to recommend for this patient's antimicrobial therapy?

ANSWER

Considering the patient's recent hospitalization, she is at risk of both community-acquired and hospital-acquired organisms. She is currently in septic shock requiring vasopressors for blood pressure support. It appears that she has been adequately resuscitated, and cultures were obtained in the ED. The next step is administering adequate broad-spectrum antimicrobials. Unfortunately, she was inadequately treated in the ED; thus, there is a delay in care for appropriate antimicrobial therapy. Considering her risk factors, potential organisms to cover include the following: *S. pneumoniae*, methicillin-sensitive *S. aureus*/MRSA, *H. influenzae*, atypical organisms, and nosocomial organisms (*P. aeruginosa*, *Klebsiella* spp., *Enterobacter* spp., *Proteus* spp., *Serratia* spp.). Reviewing local antibiograms would be ideal before initiating therapy. Empiric options would include one of the following: piperacillin/tazobactam, cefepime, meropenem, imipenem/cilastatin AND an aminoglycoside or antipseudomonal fluoroquinolone. Intravenous azithromycin should be continued for atypical coverage if no fluoroquinolone is chosen. The patient should also be initiated on either vancomycin or linezolid for potential MRSA coverage. Dosing of the penicillin antimicrobials should be aggressive, and a loading dose would be recommended before dose adjustment for renal impairment. Dosing of the aminoglycoside should take advantage of pharmacodynamic parameters and target a Cmax:MIC ratio ≥ 10. Vancomycin should be initiated with a loading dose; the maintenance dose (15 mg/kg; actual body weight) could then be initiated once vancomycin concentrations are less than 20 mg/L.

1. Lewis SJ, Mueller BA. Antibiotic dosing in patients with acute kidney injury: "enough but not too much." J Intensive Care Med 2014 Oct 16. [Epub ahead of print]

2. Tsai D, Lipman J, Roberts JA. Pharmacokinetic/pharmacodynamic considerations for the optimization of antimicrobial delivery in the critically ill. Curr Opin Crit Care 2015; 21:412-20.

Table 1-3. Common Antimicrobials Used for Initial Empiric Treatment of Sepsis

Drug	Spectrum of Activity	Dosing Regimen[a]
Piperacillin/tazobactam	Good: MSSA, streptococci, enterococci, gram negatives (including *P. aeruginosa*), anaerobes Poor: MRSA, atypicals, ESBL-producing gram negatives	Non-pseudomonal: 3.375 g IV q6hr or 4.5 g IV q8hr Pseudomonal: 3.375 g IV q4hr or 4.5 g IV q6hr
Ampicillin/sulbactam	Good: MSSA, streptococci, enterococci, gram negatives (excluding *P. aeruginosa*), anaerobes Poor: MRSA, atypicals, ESBL-producing gram negatives	1.5–3 g IV q6hr
Ceftazidime	Good: Gram negatives (including *P. aeruginosa*) Moderate: MSSA, anaerobes Poor: Streptococci, enterococci, MRSA, atypicals	1–2 g IV q8hr
Cefepime	Good: MSSA, streptococci, gram negatives (including *P. aeruginosa*) Poor: Enterococci, anaerobes, MRSA, atypicals	1–2 g IV q8hr
Imipenem/cilastatin	Good: MSSA, streptococci, anaerobes, gram negatives (including *P. aeruginosa*), ESBL-producing gram-negative rods Moderate: Enterococci Poor: MRSA, atypicals	Non-pseudomonal: 500 mg IV q6hr Pseudomonal: 1 g IV q6–8hr
Meropenem	Good: MSSA, streptococci, anaerobes, gram negatives (including *P. aeruginosa*), ESBL-producing gram-negative rods Moderate: Enterococci Poor: MRSA, atypicals	1–2 g IV q8hr
Doripenem	Good: MSSA, streptococci, anaerobes, gram negatives (including *P. aeruginosa*), ESBL-producing gram-negative rods Moderate: Enterococci Poor: MRSA, atypicals	500 mg IV q8hr

[a]Doses recommended on the basis of normal kidney and liver function.

ESBL = extended-spectrum β-lactamase; IV = intravenous(ly); MRSA = methicillin-resistant *Staphylococcus aureus*; MSSA = methicillin-sensitive *Staphylococcus aureus*; q = every.

is bacteriostatic and has increased rates of clinical failure in serious infections and bacteremia. Monobactams such as aztreonam and fluoroquinolones should not be used as empiric monotherapy because they have suboptimal activity against gram-positive organisms.

Empiric Antifungal Therapy

Empiric antifungal therapy should not routinely be added as initial empiric therapy unless the patient is at high risk of invasive candidiasis. Risk factors for invasive candidiasis include ICU admission, underlying immunosuppression, use of broad-spectrum antimicrobials, total parenteral nutrition, central venous catheters, hemodialysis, recent surgery, and damaged physiologic barriers (Pappas 2009). The most recent Infectious Diseases Society of America guidelines recommend fluconazole or an echinocandin in patients with neutropenia. Echinocandins are preferred for critically ill patients, those with recent azole exposure, and those with neutropenia and when *Candida* resistance is suspected (Pappas 2009).

Combination Therapy

Combination therapy is the use of at least two different classes of antimicrobials with different mechanisms of action (Table 1-3). Use of a β-lactam and glycopeptide (i.e., vancomycin) is not considered combination therapy because both classes exert their bactericidal activity on the bacterial cell wall. The rationale for using combination therapy as initial empiric therapy in patients with sepsis is based on the following: (1) combinations provide a broader antibacterial spectrum to cover all likely pathogens and resistant pathogens, (2) combinations (e.g., β-lactam with an aminoglycoside) can provide additive or synergistic antibacterial effects, and (3) combinations may reduce the development of drug resistance. Common antibacterial combinations in practice and in the literature include a β-lactam with an aminoglycoside, fluoroquinolone, or macrolide.

Data exist to both support and oppose the use of combination therapy. A Cochrane review consisting of 64 studies comparing β-lactam monotherapy with a β-lactam plus aminoglycoside in patients with sepsis concluded that

combination therapy did not significantly affect all-cause mortality. However, combination therapy resulted in a 70% increased risk of nephrotoxicity (Paul 2006). This risk is important to consider given that renal failure is one of the most prevalent organ dysfunctions seen in patients with severe sepsis and septic shock. A randomized, open-label, parallel-group study compared a carbapenem with or without a fluoroquinolone in patients with severe sepsis or septic shock at low risk of infection with resistant organisms. Combination therapy failed to decrease the risk of sepsis-related organ dysfunction and provided no benefit regarding other clinical outcomes (Brunkhorst 2012). A survival benefit may be seen in patients with septic shock at high risk of death/clinical failure, as evidenced by a meta-regression study (Kumar 2010).

Combination therapy should be restricted to patients with severe infections (e.g., endocarditis, gram-negative bacteremia) and high risk of death. The SSC guidelines suggest combination therapy in patients with neutropenia and those with difficult-to-treat, multidrug-resistant organisms and suggest specific combinations according to organ dysfunction and suspected organisms (Dellinger 2013).

DURATION OF ANTIMICROBIAL THERAPY AND DE-ESCALATION OF ANTIMICROBIALS

Definitive Therapy

Broad-spectrum antimicrobials should be used as initial empiric therapy in every patient with severe sepsis and septic shock. The increased mortality from initial inappropriate therapy outweighs any counter risks of drug resistance, drug cost, or drug toxicity with using broad-spectrum antimicrobials. However, all of these risks become significant if de-escalation of therapy does not occur.

De-escalation is the discontinuation of an antimicrobial agent (if not warranted) or a change from one antimicrobial to another with a narrower spectrum of activity. De-escalation is part of antimicrobial stewardship, which improves antimicrobial use and decreases resistance without compromising outcomes in ICU patients (Kaki 2011). Depending on the practice site, infectious disease consult teams may not be available or required to assist with antimicrobial stewardship. Therefore, as drug information experts, pharmacists should always be involved in de-escalation. In a retrospective study that assessed patients with hospital-acquired severe sepsis, 43% of patients achieved de-escalation, which was significantly affected by appropriate initial therapy and multitherapy. Common reasons why de-escalation was not performed included necessity of therapy because of microbiological sensitivities, lack of microbiological data, and physician reluctance because of clinical presentation (Heenen 2012). In a more recent prospective study, de-escalation of antimicrobials in patients with severe sepsis or septic shock produced a 42% lower odd of hospital mortality (p=0.026) (Garnacho-Montero 2014).

Patients, together with microbiological information, should be reassessed daily with the goal of developing a plan for definitive therapy. Clinical improvement or deterioration of the patient is used as a surrogate marker for appropriate therapy when microbiological identification is absent. Culture data can present in as early as 24 hours, usually starting with Gram stain results. Rapid bacterial identification tests such as a matrix-assisted laser desorption-ionization time-of-flight mass spectrometry and DNA-based microarray can provide information within hours of detecting positive blood cultures, but these tests are not yet widely used.

Microbiological results take 48–72 hours to complete, depending on the viability of the organism. Contacting the microbiology laboratory directly may result in definitive information sooner. Predetermined susceptibility testing should be done on all resulting organisms. Testing for susceptibility to additional drugs can also be done after discussion with the microbiology laboratory. Once microbiological identification occurs, antimicrobial therapy should be streamlined to include the most appropriate antimicrobial agent that covers the infecting organism and is safe for the patient. As stated previously, requests for susceptibility testing to additional drugs should be made before changing therapy to any antimicrobial not initially tested. Occasionally, continued use of combination antimicrobials may be indicated, even after susceptibility testing is complete, depending on the type of pathogen, patient characteristics, and favored hospital treatment regimens (Dellinger 2013).

Therapy duration for antimicrobial drugs should be determined by guideline recommendations depending on the confirmed infection source. When no confirmed source or infection is elucidated, the SSC guidelines suggest that clinical judgment and clinical information be used to guide therapy duration (Dellinger 2013). Vancomycin or another agent used to cover for MRSA is typically the first to be discontinued in the absence of microbiological data. If combination antimicrobials are given empirically, de-escalation to a single agent should be done within 3–5 days. De-escalation to a single agent should absolutely be done if no resistant bacteria are cultured. Most patients will continue on antimicrobial therapy for 7–10 days. Longer courses may be needed for patients with a slow clinical response, difficulty with source control, underlying immunosuppression, or severe infections (Dellinger 2013).

Use of Procalcitonin

Clinical biomarkers such as WBC, C-reactive protein, and erythrocyte sedimentation rate are commonly used to monitor patients with infection, but they are nonspecific for bacterial infections and do no correlate with prognosis. Inflammatory cytokines (tumor necrosis factor α, interleukin [IL]-6, and IL-8) are more specific for the presence of bacterial infection, but they are not routinely available for laboratory testing and have

limited clinical utility. Procalcitonin (PCT) is a prohormone that is essentially undetectable in healthy patients and elevated in patients with bacterial infections. Procalcitonin has been proposed to be a clinically useful prognostic biomarker in patients with sepsis when measured serially. Indeed, clearance of PCT concentrations within 24 hours of identification of severe sepsis and septic shock correlated significantly with survival in a prospective, observational cohort study. However, the initial PCT concentration did not correlate with the prognosis (de Azevedo 2015). Falsely elevated concentrations can occur in patients with autoimmune diseases, end-stage renal disease, trauma, underlying immunosuppression, and malignancy.

Monitoring PCT concentrations in patients with sepsis has an application in antimicrobial stewardship. The SSC guidelines suggest using PCT concentrations to aid in discontinuing empiric antimicrobials in patients who initially appeared to have sepsis but who have no ensuing evidence of infection (Dellinger 2013). This suggestion was based on low-quality evidence, but better-quality studies are under way that may support this recommendation. Studies show that using PCT concentrations to guide the initiation and discontinuation of empiric antimicrobial therapy leads to shorter antimicrobial durations, shorter hospital lengths of stay, and less relapse of infection with no impact on mortality (Bishop 2014; Bouadma 2010). Currently, data are preliminary regarding the benefit of incorporating routine monitoring of PCT concentrations into clinical decision-making, and few hospital laboratories can measure PCT concentrations in a timely manner.

SEPSIS BUNDLES

Overview of Bundles

Phase III of the SSC, which was thought to be the final phase, addressed guideline implementation, behavior change, and data collection. Widespread implementation of guidelines into clinical practice occurs slowly. To effect change, the SSC developed concise, time-dependent care elements for patients with severe sepsis and septic shock, termed *sepsis bundles*. The most updated versions consist of a 3- and 6-hour bundle (Dellinger 2013). Initiating antimicrobial management is an essential part of the 3-hour bundle. The SSC provides free data collection software, an implementation manual, and other tools for hospitals to use in applying the care bundles to clinical practice and measure performance. To assess the effectiveness of the bundles on a global scale, the SSC has a voluntary international registry that hospitals can use to enter patient data and monitor performance. Analysis of the registry data from January 2005 through March 2008 showed increased compliance with the bundles and decreased hospital mortality from 37.0% to 30.8% in 2 years (Levy 2010). The bundles were fully completed for only 1 of every 5 patients. Potential barriers to compliance are disagreement on the definitions of sepsis, increased workload, staffing shortages, lack of resources for protocol development and implementation, and lack of collaboration among health care providers (Kissoon 2014). Regarding antimicrobial therapy, 67% of patients received broad-spectrum antimicrobials within the 6-hour period, which was associated with a 22% risk reduction in hospital mortality (Levy 2010).

The benefits of adherence to the sepsis bundles were evident, yet they are still not the standard of care. In addition, the SSC had failed to meet its goal of a 25% mortality reduction by 2009. Therefore, phase IV was implemented to reinvigorate the campaign. The SSC declaration, which presented concurrently with the third edition of the SSC guidelines, charged clinicians to recommit to the original goals of the campaign. New goals were added as the result of data gathered in phases I–III. Phase III analysis identified increased mortality in patients admitted to the ICU from the floor compared with those admitted to the ICU from the ED. The SSC has collaborated with U.S. hospitals to target management on hospital floors. Performance improvement programs are being created with an emphasis on sepsis screening, early identification, and initiation of the 3-hour bundle on the floors. Other efforts are being made to update the hemodynamic bundle, given the results from three recent clinical trials and work with national regulatory bodies to mandate the sepsis bundles in clinical practice.

CONCLUSION

Sepsis continues to be a significant cause of mortality and morbidity. Rapid identification and treatment of the patient with sepsis is vital to improve outcomes. Early and appropriate antimicrobial therapy is an essential component of sepsis care. Pharmacokinetic and pharmacodynamic data should be used to optimize antimicrobial therapy and, when possible, individualize therapy. Critical care pharmacists play an essential role in developing effective antimicrobial treatment regimens, promoting good antimicrobial stewardship, developing institutional sepsis protocols, and educating on the proper use of antimicrobials.

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Practice Points

In determining the optimal pharmacotherapy for antimicrobial management in patients with sepsis, practitioners should consider the following:

- **Routine screening for early identification of sepsis should be done in any patient with SIRS and known or suspected infection, and further evaluation should consider severe sepsis or septic shock.**
- **At least two blood cultures should be obtained before initiating antimicrobials, but this should not delay prompt administration of therapy.**
- **Source control should identify potential infection sites and eliminate the source, whenever possible.**
- **Initial empiric antimicrobial therapy should be administered within 1–3 hours of sepsis recognition and include one or more drugs with activity against all likely pathogens.**
- **Alterations in pharmacokinetics and pharmacodynamics because of sepsis should be incorporated into the design of effective and safe antimicrobial therapy.**
- **Patient and microbiological information should be reassessed daily with the goal of de-escalating and determining definitive therapy.**

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Self-Assessment Questions

Questions 1 and 2 pertain to the following case.

J.T. is an 84-year-old man brought to the ED by ambulance from his long-term care facility. The nursing staff there said that J.T. has been confused and incontinent of urine for the past 3 days, which is not normal for him. His medical history is significant for hypertension, history of transient ischemic attack, dementia, and benign prostatic hyperplasia. His vital signs in the ED were temperature 100.2°F (37.9°C), blood pressure 130/64 mm Hg, heart rate 102 beats/minute, and respiratory rate 20 breaths/minute. A urinary catheter was placed, and a urinalysis revealed the following: urine-specific gravity 1.030, moderate leukocyte esterase, negative nitrite, 11 RBCs per high-power field (HPF), 10–12 WBCs/HPF, 3–5 squamous epithelial cells/HPF, and few bacteria. Because of his worsening mental status and inability to protect his airway, J.T. was intubated and transferred to the medical ICU. His initial laboratory data showed the following: K 4.4 mmol/L, SCr 2.0 mg/dL (baseline SCr 1.5 mg/dL), BUN 40 mg/dL, WBC 11 x 10^3 cells/mm^3, albumin 3.1 g/dL, and lactate 0.9 mmol/L. In the ICU, a central venous catheter was placed in his right internal jugular vein, which measured a central venous pressure of 9 mm Hg.

1. Based on the latest criteria for sepsis, which one of the following terms best describes J.T.'s current condition?

   A. Systemic inflammatory response syndrome (SIRS)
   B. Sepsis
   C. Severe sepsis
   D. Septic shock

2. J.T.'s clinical status deteriorates, and he is now hypotensive. He has received 3 L of crystalloid solution, and his heart rate is 110 beats/minute and mean arterial blood pressure is 60 mm Hg. Laboratory tests are repeated with the following results: K 4.7 mmol/L, SCr 2.3 mg/dL, BUN 48 mg/dL, WBC 15 x 10^3 cells/mm^3, albumin 2.8 g/dL, and lactate 4.5 mmol/L. According to the latest criteria for sepsis, which one of the following best describes J.T.'s current condition?

   A. SIRS
   B. Sepsis
   C. Severe sepsis
   D. Septic shock

Questions 3 and 4 pertain to the following case.

J.E. is a 58-year-old man with a medical history of end-stage renal disease from uncontrolled hypertension, depression, and coronary artery disease. J.E.'s family brought him to the ED this morning after noticing that he seemed confused. He has pain in his right arm that began 2 days ago. Twenty-four hours before he presented, J.E. noticed his right arm was more red/swollen and tender to the touch at his atriovenous (AV) fistula site. He was also febrile and had rigors.

3. Which one of the following would best help identify potential sources of J.E.'s infection?

   A. Blood cultures
   B. Blood and sputum cultures
   C. Blood, sputum, and urinary cultures
   D. Blood, sputum, and CSF cultures

4. Which one of the following interventions is best to recommend for J.E.?

   A. Remove AV fistula.
   B. Administer broad-spectrum empiric antibiotics and remove AV fistula.
   C. Administer broad-spectrum empiric antibiotics.
   D. Administer broad-spectrum empiric antibiotics; then evaluate AV fistula for possible drainage or removal within 12 hours.

Questions 5–8 pertain to the following case.

E.M. is a 34-year-old man (height 71 inches, weight 83 kg) who presents to the ED with a history of fever, chills, and productive cough. He has had 3–4 days of malaise, shortness of breath, and fever. E.M. was seen in an outpatient clinic 2 days ago and initiated on oseltamivir for possible seasonal influenza. In the ED, he is confused and develops hypoxic respiratory failure and refractory shock, which requires mechanical intubation, 4 L of crystalloid solution, and a norepinephrine continuous infusion. His vital signs are temperature 104.1°F (40.1°C), blood pressure 100/61 mm Hg, heart rate 90 beats/minute, respiratory rate 31 breaths/minute, and SaO_2 91% on 80% Fio_2. His laboratory data are as follows: Na 147 mEq/L, K 4.3 mEq/L, Cl 108 mEq/L, bicarbonate 18 mEq/L, BUN 31 mg/dL, SCr 1.9 mg/dL, glucose 126 mg/dL, PT 13.4 seconds, INR 1.6, and lactate 6.9 mmol/L. His urine output is 10 mL/hour.

5. Which one of the following statements best describes the pharmacokinetics of meropenem in E.M.?

   A. Volume of distribution will be increased; clearance will be decreased.
   B. Volume of distribution will be increased; clearance will be increased.
   C. Volume of distribution will be unchanged; clearance will be decreased.
   D. Volume of distribution will be unchanged; clearance will be increased.

6. Which one of the following statements best describes the pharmacokinetic of levofloxacin in E.M.?

   A. Volume of distribution will be increased; clearance will be decreased.
   B. Volume of distribution will be increased; clearance will be increased.

C. Volume of distribution will be unchanged; clearance will be decreased.
D. Volume of distribution will be unchanged; clearance will be increased.

7. Which one of the following regimens best optimizes the pharmacodynamic properties of the chosen drug for E.M while decreasing risk of toxicity?

   A. Meropenem loading dose of 2000 mg; then 500 mg intravenously every 48 hours
   B. Cefepime loading dose of 2000 mg; then 2000 mg intravenously every 12 hours
   C. Levofloxacin loading dose of 500 mg; then 250 mg intravenously every 24 hours
   D. Piperacillin/tazobactam loading dose of 4.5 g; then 2.25 g intravenously every 6 hours

8. Which one of the following regimens best optimizes the pharmacodynamic properties of vancomycin for E.M.?

   A. Vancomycin 1250 mg intravenously every 24 hours
   B. Vancomycin 2500 mg intravenously once; then 1000 mg intravenously every 24 hours
   C. Vancomycin 2500 mg intravenously once; then 1250 mg when vancomycin concentration is less than 20 mg/L
   D. Vancomycin 2500 mg intravenously once; then 1250 mg intravenously every 24 hours

Questions 9 and 10 pertain to the following case.

M.R. is a 56-year-old woman (height 66 inches, weight 100 kg) who presents to the ED with severe acute respiratory distress syndrome, septic shock, and acute renal failure. She has a medical history of repeated hospitalizations and recurrent infections with multidrug resistant organisms, hypertension, chronic obstructive pulmonary disease (COPD), and depression. M.R. is intubated for hypoxic respiratory failure and initiated on continuous venovenous hemofiltration. Her vital signs are temperature 102.9°F (39.4°C), blood pressure 110/55 mm Hg, heart rate 115 beats/minute, respiratory rate 28 breaths/minute, and Sao_2 92% on 100% FiO_2. Her laboratory test results include Na 130 mEq/L, K 3.7 mEq/L, Cl 99 mEq/L, bicarbonate 16 mEq/L, BUN 28 mg/dL, SCr 2.7 mg/dL, and glucose 148 mg/dL. Lactate is 4.5 mmol/L, and urine output is 20 mL/hour. Blood cultures are positive for a non–lactose-fermenting, gram-negative rod, oxidase negative. Chest radiography shows diffuse infiltrates without effusions.

9. Which one of the following cultures would best help identify potential infection sources in M.R.?

   A. Blood cultures
   B. Blood and sputum cultures
   C. Blood, sputum, and urinary cultures
   D. Blood, sputum, and pleural cultures

10. In addition to meropenem therapy, which one of the following empiric antibiotic regimens would be best to recommend for M.R.?

    A. Colistimethate sodium 130 mg intravenously every 12 hours plus colistimethate sodium 150 mg inhaled every 12 hours
    B. Colistimethate sodium 270 mg intravenously once; then 130 mg intravenously every 48 hours
    C. Polymyxin B 1.25 million units once; then 1.25 million units intravenously every 24 hours
    D. Polymyxin B 1.25 million units intravenously every 12 hours and colistimethate sodium 150 mg inhaled every 12 hours

11. Which one of the following descriptions best defines the pharmacodynamic properties of polymyxin?

    A. $AUC_{0\text{-}24}$/MIC.
    B. 50%–70% *f*T>MIC.
    C. Greater than 400 $AUC_{0\text{-}24}$/MIC.
    D. Greater than 10 x MIC.

Questions 12–14 pertain to the following case.

J.P. is a 72-year-old man admitted to the medical ICU from the ED with septic shock. His medical history is significant for hypertension, Parkinson disease, and prostate cancer (radical prostatectomy 20 years ago). J.P. resides in a nursing home. His laboratory test results are as follows: bicarbonate 18 mg/dL, SCr 1.8 mg/dL, BUN 37 mg/dL, WBC 14.7 x 10^3 cells/mm^3, and lactate 5.3 mmol/L. A urinalysis reveals WBC greater than 100 cells/HPF, nitrite positive, leukocyte esterase positive, and moderate bacteria. J.P. receives early goal-directed therapy of the following: 3 L of crystalloid fluid resuscitation, norepinephrine, and broad-spectrum antibiotics (cefepime and vancomycin). His vital signs are temperature 101.5°F (38.6°C), blood pressure 100/70 mm Hg on norepinephrine 8 mcg/minute, heart rate 90 beats/minute, and respiratory rate 22 breaths/minute on mechanical ventilation. J.P. is continued on cefepime and vancomycin.

12. The medical resident notes that J.P.'s urine was colonized with *Candida* on a past admission and is concerned that the patient is not being covered for fungal infections. Which one of the following is best to recommend regarding empiric antifungal therapy for J.P.?

    A. One dose of antifungal therapy should be given to increase the chance of appropriate initial antimicrobial therapy.
    B. Antifungal therapy should be added because the patient is receiving broad-spectrum antibiotics.
    C. Antifungal therapy should be added because the patient is in septic shock.
    D. Antifungal therapy should not be added because the patient is not at high risk of invasive candidiasis.

13. It has been 48 hours since J.P. was initiated on antibiotics. He no longer requires vasopressor support, his repeat lactate is 1.1 mmol/L, and he has not been febrile in 24 hours. He is still receiving cefepime and vancomycin. Blood cultures obtained before antibiotic administration are growing lactose-fermenting, gram-negative rods. Urine culture also obtained before antibiotics has resulted in *Escherichia coli*, antibiotic susceptibilities pending. Which one of the following is best to recommend regarding J.P.'s antimicrobial therapy?

    A. Continue current antibiotics.
    B. Continue cefepime alone.
    C. Change to ceftriaxone alone.
    D. Add ciprofloxacin and discontinue vancomycin.

14. The following day, speciation and susceptibilities of J.P.'s cultures are finalized. Blood and urine cultures are growing *E. coli* with identical susceptibilities (shown in the following table).

Blood: *E. coli*

Drug	MIC Interpretation
Ampicillin	R
Cefazolin	I
Cefepime	S
Ceftriaxone	S
Ciprofloxacin	R
Levofloxacin	I
Meropenem	S
Piperacillin/tazobactam	S

    Repeat blood cultures are negative. Which one of the following is the most appropriate intravenous regimen to recommend for J.P.?

    A. Cefepime
    B. Meropenem
    C. Cefazolin
    D. Ceftriaxone

15. A 55-year-old man with a medical history of end-stage renal disease resulting in renal transplant 6 years ago (on immunosuppression), diabetes mellitus, and nonischemic cardiomyopathy with an ejection fraction of 50% presents to the ED with a 1-week history of malaise, productive cough, body aches, and subjective fevers. Vital signs in the ED are temperature 101.1°F (38.4°C), blood pressure 100/72 mm Hg, heart rate 108 beats/minute, and respiratory rate 16 breaths/minute. The patient tested negative for the rapid influenza test. Chest radiography and urinalysis are negative. Physical examination reveals a large area of induration and redness on his right lower extremity that is tender and warm to the touch. His initial laboratory results are as follows: K 4.5 mEq/L, SCr 2.5 mg/dL (baseline 1.5 mg/dL), BUN 30 mg/dL, glucose 230 mg/dL, and WBC 13.2 x 10^3 cells/mm^3. In the ED, the patient becomes hypotensive (blood pressure 80/60 mm Hg), and he is given 2 L intravenous crystalloid with a subsequent blood pressure of 90/68 mm Hg. Blood cultures are obtained, and the patient is admitted to the medical ICU. Which one of the following is best to recommend for initial empiric therapy in this patient?

    A. Meropenem and vancomycin
    B. Clindamycin alone
    C. Piperacillin/tazobactam alone
    D. Ceftriaxone and clindamycin

16. A 30-year-old man with a history of diabetes and alcohol abuse is admitted to the general medicine floor for a GI bleed. On hospital day 1, endoscopy reveals several nonbleeding duodenal polyps that are resected. The procedure is complicated by brisk arterial bleeding after resection, controlled with clips and epinephrine injections. The gastroenterologist notes a deep defect in the mucosal wall. The patient is sent back to the general medicine floor for observation. That evening, the patient has severe abdominal pain and vomiting. His vital signs on examination are temperature 101.7°F (38.7°C), blood pressure 160/88 mm Hg, heart rate 99 beats/minute, and respiratory rate 24 breaths/minute. Physical examination reveals rebound tenderness and decreased bowel sounds. Laboratory tests results are WBC 14.1 x 10^3 cells/mm^3 and lactate 1.7 mmol/L. Surveillance cultures on admission are negative for MRSA. The overnight resident becomes concerned for postoperative peritonitis and calls the gastroenterologist for an emergency exploratory laparotomy. Which one of the following is best to recommend regarding initial empiric antimicrobial therapy for this patient?

    A. Metronidazole and vancomycin
    B. Meropenem and vancomycin
    C. Ceftriaxone alone
    D. Piperacillin/tazobactam

17. A 50-year-old woman is transferred from an outside hospital with hypoxic respiratory failure and septic shock from suspected pneumonia. Her history is significant for COPD and diabetes. Her home drugs include budesonide/formoterol 160 mcg/4.5 mcg 2 inhalations twice daily, tiotropium 18 mcg 1 inhalation daily, albuterol 90 mcg 2 puffs every 6 hours as needed, and NPH (neutral protamine Hagedorn) insulin 10 units subcutaneously twice daily. She has a documented allergy to penicillin, reaction unknown. Three months ago, the patient was admitted to the outside hospital for a COPD exacerbation and treated with a 1-week prednisone burst. The patient was also given an 8-day course of ciprofloxacin after her sputum culture grew *Pseudomonas aeruginosa*. At the outside hospital, sputum and blood cultures were obtained.

She received one dose of intravenous levofloxacin 750 mg and 4 L of intravenous crystalloid with subsequent blood pressures of 80–90/50–60 mm Hg; therefore, a norepinephrine drip was initiated and titrated to 10 mcg/minute to achieve mean arterial pressure (MAP) values greater than 65 mm Hg. On arrival to the MICU, her MAP values were 60–64 mm Hg; she was given another 1-L bolus of intravenous crystalloid, norepinephrine was titrated to 14 mcg/minute, and vasopressin was added at 0.04 unit/minute. Which one of the following, in addition to vancomycin, is best to recommend for this patient's initial empiric antimicrobial therapy?

A. Piperacillin/tazobactam and amikacin
B. Cefepime and amikacin
C. Ceftriaxone and levofloxacin
D. Meropenem and ciprofloxacin

18. The ICU director has asked you to give an in-service to the medicine residents on the importance of timely and appropriate antimicrobial therapy in patients with suspected sepsis. He gave the residents a recently published retrospective review examining combination antibiotic therapy in patients with septic shock; now, he wants you to help the staff analyze the results. The study included 4662 patients divided into monotherapy versus combination therapy groups and looked at 28-day mortality. In the monotherapy group, 1277 of 2948 patients died. In the combination group, 461 of 1714 patients died. According to the study-specific number needed to treat (NNT), which one of the following is the best summary to present to the medicine residents?

A. NNT = 6; combination antibiotic therapy is efficacious in preventing 28-day mortality in patients with septic shock.
B. NNT = 0.06; combination antibiotic therapy should be used for all patients with septic shock to increase survival.
C. NNT = 62; combination antibiotic therapy is efficacious in preventing 28-day mortality in patients with septic shock.
D. NNT = 162; combination antibiotic therapy should not be used for any patients with septic shock to increase survival.

19. A 47-year-old woman is admitted to the MICU from the ED with septic shock and altered mental status. Her medical history is significant for quadriplegia after a motor vehicle crash (6 years ago), respiratory failure status post tracheostomy (not on supplemental oxygen), neurogenic bladder with suprapubic catheter, and recurrent UTIs. On arrival to the ED, she is unresponsive with a blood pressure of 74/56 mm Hg. A left femoral triple-lumen central venous catheter is placed, and she is given 2 L of intravenous crystalloid with minimal response in blood pressure; therefore, norepinephrine is initiated at 5 mcg/minute. Cultures for blood, urine, and respiratory (by endotracheal aspirate) are obtained. Urinalysis reveals the following: greater than 100 WBCs/HPF, greater than 100 RBCs/HPF, and many bacteria. Initial laboratory test results are as follows: SCr 1.04 mg/dL (baseline 0.3 mg/dL), BUN 82 mg/dL, phosphorus 6.9 mg/dL, WBC 20 x 10^3 cells/mm^3, and lactate 6.1 mmol/L. Chest radiography reveals right basilar opacities favoring atelectasis, although a component of infection/aspiration might also be considered. Previous microbiological data evaluations (within the past 6 months) are shown in the following table:

Urine: > 100,000 CFU/mL *P. aeruginosa*		**Urine: > 100,000 CFU/mL *E. coli***		**Blood: (1/2) *S. aureus***	
Drug	MIC Interpretation	Drug	MIC Interpretation	Drug	MIC Interpretation
Cefepime	S	Ampicillin	R	Erythromycin	R
Ciprofloxacin	I	Cefepime	S	Oxacillin	R
Levofloxacin	I	Ceftriaxone	S	Sulfamethoxazole/ trimethoprim	S
Meropenem	S	Ciprofloxacin	R	Vancomycin	S
Piperacillin/ tazobactam	S	Gentamicin	S		
		Levofloxacin	I		
		Meropenem	S		
		Piperacillin/ tazobactam	S		
		Sulfamethoxazole/ trimethoprim	S		

Which one of the following is best to recommend as initial empiric therapy for this patient?

A. Piperacillin/tazobactam, levofloxacin, and vancomycin
B. Meropenem, gentamicin, and vancomycin
C. Meropenem and sulfamethoxazole/trimethoprim
D. Piperacillin/tazobactam, gentamicin, and linezolid

20. In your work in a community hospital, you are asked to join the sepsis committee. One of the main charges of this committee is to develop a sepsis treatment pathway to help improve the quality of care. Your recommendation is to design and implement a sepsis bundle. Given the available evidence, which one of the following components is best to include in the sepsis bundle to help improve mortality and the duration of hospitalization?

A. Providing antimicrobial stewardship
B. Obtaining blood cultures before administering antimicrobials
C. Administering broad-spectrum antimicrobials
D. Giving norepinephrine as the initial vasopressor of choice

Learner Chapter Evaluation: Sepsis.

As you take the posttest for this chapter, also evaluate the material's quality and usefulness, as well as the achievement of learning objectives. Rate each item using this 5-point scale:

- Strongly agree
- Agree
- Neutral
- Disagree
- Strongly disagree

1. The content of the chapter met my educational needs.
2. The content of the chapter satisfied my expectations.
3. The author presented the chapter content effectively.
4. The content of the chapter was relevant to my practice and presented at the appropriate depth and scope.
5. The content of the chapter was objective and balanced.
6. The content of the chapter is free of bias, promotion, or advertisement of commercial products.
7. The content of the chapter was useful to me.
8. The teaching and learning methods used in the chapter were effective.
9. The active learning methods used in the chapter were effective.
10. The learning assessment activities used in the chapter were effective.
11. The chapter was effective overall.

Use the 5-point scale to indicate whether this chapter prepared you to accomplish the following learning objectives:

12. Evaluate a patient for suspected sepsis, severe sepsis, or septic shock, identifying potential infection sites and using proper source control.
13. Distinguish pharmacokinetic and pharmacodynamic changes in the patient with sepsis to optimize antimicrobial treatment.
14. Design appropriate empiric antimicrobial therapy, including combination antimicrobial therapy when justified, in the patient with sepsis.
15. Justify de-escalation of antimicrobial therapy using patient and culture data.
16. Apply sepsis bundles to facilitate early antimicrobial therapy and demonstrate good antimicrobial stewardship.
17. Please provide any specific comments related to any perceptions of bias, promotion, or advertisement of commercial products.
18. Please expand on any of your above responses, and/or provide any additional comments regarding this chapter:

Antimicrobial Stewardship in the ICU

By Anthony J. Guarascio, Pharm.D., BCPS

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LEARNING OBJECTIVES

1. Analyze key antimicrobial stewardship (AMS) principles and determine how they can be applied in the ICU.
2. Design empiric antimicrobial treatment regimens for patients at risk of multidrug resistant pathogens and assess treatment courses for opportunities to optimize therapy.
3. Justify the use of rapid diagnostic technology for AMS and detect limitations for their use.
4. Distinguish differences between the clinical utility and characteristics of the biomarkers procalcitonin and C-reactive protein.
5. Evaluate antimicrobial therapy for a patient in both defined daily dose and days of therapy metrics and describe the role of antimicrobial consumption in drug resistance.

ABBREVIATIONS IN THIS CHAPTER

AMS	Antimicrobial stewardship
CRP	C-reactive protein
DDD	Defined daily dose
DOT	Days of therapy
fT>MIC	Free drug concentrations above the MIC
HAP/VAP	Hospital-acquired pneumonia/ventilator-associated pneumonia
ID	Infectious diseases
IDSA	Infectious Diseases Society of America
MDR	Multidrug resistant
PCT	Procalcitonin
VAP	Ventilator-associated pneumonia

INTRODUCTION

The guiding principle of antimicrobial stewardship (AMS) is to implement optimal antimicrobial treatment regimens in order to achieve positive clinical outcomes while reducing subsequent emergence of antimicrobial resistant organisms. As much as 50% of antimicrobial use in the hospital setting has been described as inappropriate (Hecker 2003). Additionally, some reports suggest that the ICU setting is responsible for up to a 10-fold greater use of antimicrobial agents than general hospital units (Roder 1993). A substantial portion of this antimicrobial use may simply be attributed to standard care for complex and acutely ill patients in critical care settings. Nevertheless, as the ICU continues to be a focal point for high antimicrobial use, it has become a critical location for the development and concentration of AMS efforts.

An overwhelming amount of evidence links overuse of antimicrobials and resulting collateral damage in the health care setting, most notably manifesting as the rapid development of antimicrobial resistance. Increasing patient exposure to antimicrobials leads to colonization with resistant organisms, increasing the likelihood of infection with drug-resistant organisms. As expected because of greater antimicrobial utilization, resistance rates tend to be more pronounced in ICU settings versus the general hospital. In addition to increasing resistance rates, inappropriate and excessive antimicrobial use has been shown to negatively affect ICU length of stay, mortality rates, and health care costs. These factors form the basis for the essential need for AMS initiatives in the critical care setting.

IDSA Guidelines for Antimicrobial Stewardship

The Infectious Diseases Society of America (IDSA) has established guidelines for developing institutional processes that support AMS initiatives (Dellit 2007). The document focuses on hospital-based stewardship programs, and most data used in the guideline are derived from adult patients in the ICU setting. The IDSA AMS guidelines describe various stewardship interventions, with recommendations for their use or avoidance as part of a stewardship program (Table 2-1). These guidelines are not intended for use as a static one size fits all model; rather, modifications can be made for institution-specific needs and overall structure of clinical services.

Application of Antimicrobial Stewardship Principles in the ICU

Critical care units are one of the most dynamic hospital locations, where fast-paced clinical decisions are made and broad-spectrum antimicrobial regimens are often selected to cover potentially serious pathogens. The stakes are high because patient survival is associated with early, appropriate antimicrobial therapy. For this reason, the ICU presents a particular challenge for the implementation of AMS. Broad-spectrum therapy is often necessary for initial treatment; however, judicious use and prompt follow-up is also required to curtail unwarranted antimicrobial use. The balancing act between promoting positive clinical outcomes and fostering prudent antimicrobial use is challenging, but the IDSA AMS guidelines can serve as a model for institutional implementation.

BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:

- Baseline knowledge of antimicrobial stewardship interventions
- Proper treatment of common infections encountered in the ICU such as hospital-acquired pneumonia and sepsis
- General principles of pharmacodynamic dose optimization of antimicrobial agents
- Baseline understanding of antibiograms and drug resistance characteristics
- Knowledge of hospital policy and protocol development in regard to antimicrobial use

ADDITIONAL READINGS

The following free resources have additional background information on this topic:

- CDC Get Smart for Healthcare. Core Elements of Hospital Antibiotic Stewardship Program
- CDC and Institute for Healthcare Improvement Antibiotic Stewardship Driver Diagram.
- Society for Healthcare Epidemiology of America (SHEA), Infectious Diseases Society of America (IDSA) and Pediatric Infectious Diseases Society (PIDS) Policy Statement on Antimicrobial Stewardship. Infect Control Hosp Epidemiol 2015;30:322–27.
- The Joint Commission. Antimicrobial Stewardship Toolkit Oak Brook, IL: Joint Commission Resources, 2012.

CORE ANTIMICROBIAL STEWARDSHIP PROCESSES IN THE ICU

Although AMS in the ICU can take various forms, the two core processes of *prospective audit with intervention and feedback* and *formulary restriction* at various levels are mainstays. In the past decade, AMS processes in the ICU have evolved from a more restrictive mentality to an emphasis on timely facilitation of appropriate therapy (Martin 2011). Advances in health care information technology have facilitated the standardization and efficiency of appropriate initial therapy through computerized implementation of guidelines and clinical pathways. Because of this progression, importance has been placed on prompt follow-up and intervention with feedback when necessary. Particular attention has been focused on opportunities for antimicrobial de-escalation, dose optimization, and discontinuation of therapy. Because of the lack of enteral access or as a result of GI absorption issues with many patients in the ICU, parenteral-to-oral conversion opportunities are often significantly reduced when compared with general hospital wards (Candeloro 2012).

Prospective Audit of Antimicrobial Use with Intervention and Feedback

Prospective audit with intervention and feedback serves as a gateway for the implementation of various other AMS principles. The hallmark of this intervention is regular and consistent reassessments of antimicrobial treatment plans with proper communication. Daily review of antimicrobial use is optimal; however, if resources are limited, even a scaled-down version (i.e., two or three reviews weekly) can have a positive impact on patient outcomes. Subsequent verbal or written communication to prescribers is performed when interventions are made to optimize or discontinue therapy. Furthermore, occasional AMS rounds between stewardship staff and ICU practitioners may remove barriers to effective communication and implementation of stewardship initiatives (Drew 2009). Although this intervention can be described as a "back-end approach" that does not fully capture the point-of-order entry, it helps facilitate upfront therapy without

Table 2-1. Summary of IDSA Guideline Interventions and Outcomes for Antimicrobial Stewardship

Intervention	Description	Key Outcome(s) (level of evidence)
Core Intervention: Prospective audit with intervention and feedback	Audit of antimicrobial use with direct interaction and feedback to prescriber	Reduction in inappropriate antimicrobial use (A-I)
Core Intervention: Formulary restriction and preauthorization	Restriction of broad-spectrum antimicrobials by formulary limitation or requirement of justification for use	Restriction lowers antimicrobial use and cost (A-I), however limiting use of only select agent(s) may shift resistance to alternative agents (B-II)
Clinician Education	Conference presentations, house staff teaching sessions, promotion of educational materials or order forms	Education is an essential element to influence prescribing behavior (A-III) but must be combined with core interventions to provide sustained impact on prescribing practices (B-II)
Guidelines and Clinical Pathways	Implementation of clinical guidelines tailored to local microbiology and patient data	Multidisciplinary development of evidence-based guidelines using local microbiology and resistance patterns improves antimicrobial utilization (A-I)
De-escalation or Streamlining therapy	Targeting causative pathogens based off of culture results	Decreased antimicrobial exposure and cost savings (A-II)
Dose optimization	Use of pharmacokinetic/ pharmacodynamic parameters, patient characteristics, and microbiologic findings	Dose optimization is a necessary component of stewardship to enhance activity of antimicrobials (A-II)
Parenteral to oral conversion	Development of clinical criteria for oral conversion of antimicrobials with excellent oral bioavailability	Parenteral to oral conversion can decrease length of hospital stay and health care costs (A-I)
Antimicrobial order forms	Use of order forms with automatic stop orders or requiring physician justification of antimicrobial use	Antimicrobial order forms can be an effective means of implementing stewardship (B-II)
Antimicrobial cycling	Antimicrobials are substituted for one another at regular intervals	Insufficient data to recommend antimicrobial cycling as a means of reducing resistance (C-II). Transient decrease in selection pressure rebounds on antimicrobial re-exposure.
Combination therapy	Using two antimicrobial agents for coverage of multi-drug resistant pathogens	Combination therapy can increase the likelihood of empiric coverage (A-II) but data are insufficient for prevention of resistance (C-II)

A-I = Good evidence to support a recommendation for use; evidence from ≥1 randomized, controlled trial.

A-II = Good evidence to support a recommendation for use; evidence from ≥1 well designed clinical trial without randomization; from cohort or case controlled analytic studies (preferably from more than one center); multiple time series; or from dramatic results from uncontrolled experiments.

A-III = Good evidence to support a recommendation for use; evidence from expert opinion or descriptive studies.

B-II = Moderate evidence to support a recommendation for use; evidence from ≥1 well designed clinical trial without randomization.

C-II = Poor evidence to support a recommendation for use; evidence from ≥1 well designed clinical trial without randomization.

Information from: Dellit TH, Owens RC, McGowen JE, et al. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. Clin Infect Dis 2007;44:159-77.

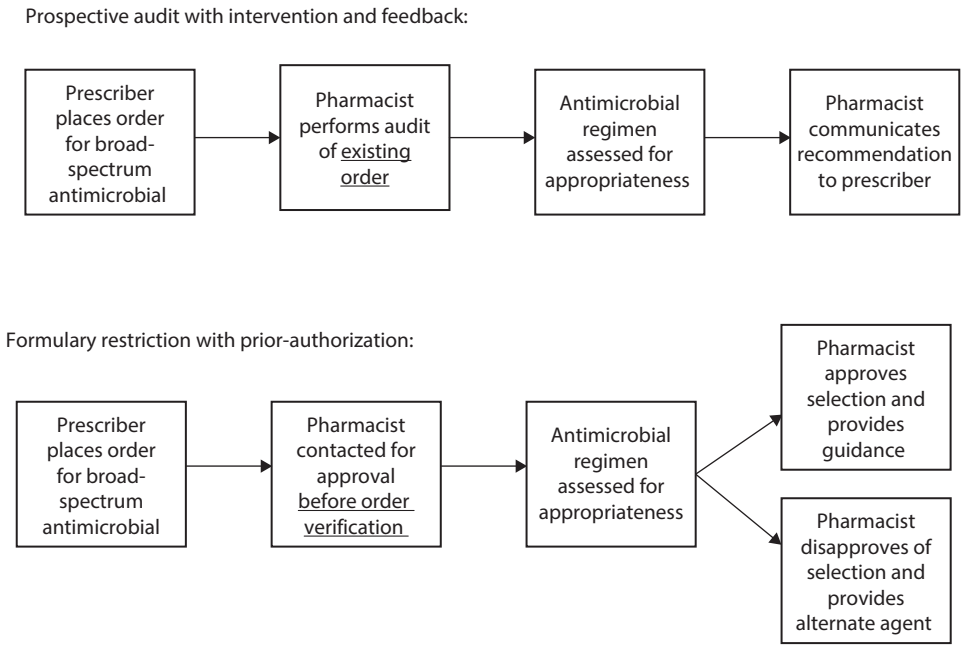

Figure 2-1. Comparison of the step-wise process of two approaches to antimicrobial stewardship in the ICU: (1) the pharmacist-initiated prospective audit with feedback; and (2) the formulary restriction with prior-authorization

delay and ensures proper follow-up (Figure 2-1). Particular attention is often devoted to broad-spectrum empiric antimicrobial regimens that pose the greatest risk of development of drug resistance.

Studies have estimated that only 25% of ICU patients who receive empiric antimicrobials are confirmed to have infection (Claridge 2010), highlighting the need for prospective follow-up and discontinuation of unnecessary therapy. A recent quasi-experimental study performed in a medical and surgical ICU described daily prospective audit and feedback through collaboration between an infectious disease (ID) physician, ID pharmacist, and critical care pharmacist. This intervention significantly increased the rate of appropriate antimicrobial selection (78% vs. 70%, p=0.042), lowered the emergence of antimicrobial-resistant pathogens (25% vs. 31%, p=0.033), and was independently associated with appropriate therapy and reduced antimicrobial resistance (odds ratio [OR]=0.42; 95% CI, 0.27–0.67) (DiazGranados 2012). It is important to note that although the role of the ID physician varied throughout the study, a critical care pharmacist rounded consistently with the ICU team to facilitate proper communication of AMS recommendations.

Multiple methods for data analysis within the electronic medical record exist. Computerized surveillance software and clinical decision support systems can be effective audit tools to help identify deviations from antimicrobial appropriateness on a larger scale (e.g., house-wide or unit-wide surveillance). They function as a continuum of intelligently filtered information within the electronic health care record and offer feedback regarding potential opportunities for antimicrobial therapy intervention.

One of the earliest studies assessing use of a computerized device for decision support in the ICU described a significant reduction in the number of antimicrobial choice-susceptibility mismatches (12 vs. 206, p<0.01) and in the number of adverse events caused by antimicrobials (4 vs. 28, p<0.02) (Evans 1998). The use of a different clinical decision support system facilitated a notable reduction in resistance rates for multidrug resistant (MDR) pathogens over a 7-year period in a time-series analysis (Yong 2010). In a more recent study, automated alerts led to reductions in time to appropriate therapy (8 vs. 14 hours, p=0.14) along with an independent reduction in length of stay of 2.2 days in patients with gram-negative bacteremia (Pogue 2014). The use of clinical decision support systems expands the depth and breadth of AMS initiatives and ultimately fosters the achievement of positive patient outcomes.

Formulary Restriction and Approved Use Criteria

Formulary restriction is another primary strategy for implementation of AMS. Prior authorization requires prescribers to obtain approval by ID or AMS practitioners before initiating certain broad-spectrum agents. In many circumstances, an AMS team member carries a dedicated pager or telephone

to receive antimicrobial approval requests. Restrictions can be integrated into computerized physician order-entry systems to control antimicrobial agent use during the ordering process. Difficulties with this approach include the significant time and resources dedicated to agent approval and the limited antimicrobial selection for prescribers. Prior authorization may cause inadvertent consequences such as increased use of alternative antimicrobials as well as delays in initiating therapy without prompt communication (Drew 2009). There are also concerns that a loss of prescriptive autonomy can significantly strain relationships between clinicians and AMS staff rather than encourage a collaborative approach. Alternatively, an initial approval window (e.g., 24–48 hours) can be implemented as a time during which approval is only required for continuation of therapy beyond the window, allowing for discussion between AMS staff and the ordering service (Drew 2009).

Although restriction is an effective means of reducing antimicrobial consumption, criteria that are too restrictive can be likened to the analogy of squeezing a balloon—the restriction of one particular agent causes a compensatory rise in use and resistance of a second agent (Burke 1998). A study illustrated that near-absolute restriction of the cephalosporin class achieved its primary end point of reducing cephalosporin-resistant *Klebsiella* spp. by 71% in the ICU; however, this achievement occurred at the expense of a 695 increase in imipenem-resistant *Pseudomonas aeruginosa* (Rahal 1998). These findings highlight the importance of restriction efforts that focus on reducing total antimicrobial consumption for broad-spectrum antimicrobials within different classes rather than focusing specifically on a single antimicrobial agent.

Use of Clinical Guidelines and Pathways

Clinical guidelines and pathways standardize the evidence-based antimicrobial prescribing processes. Clinical guidelines can take both paper and electronic formats, whereas pathways are typically built directly into the order-entry process for electronic medical records. Collaboration between ID clinicians, ICU physicians, and critical care pharmacists is important in the development and implementation of clinical guidelines (Owens 2009).

Implementation of one such clinical guideline for pneumonia in the ICU reduced ICU length of stay (20.2 days vs. 12.0 days, p=0.001), duration of mechanical ventilation (318 hours vs. 178 hours, p=0.017) and mean duration of antimicrobial treatment (10 days vs. 6 days, p=0.001) (Nachtigall 2009).

The most sophisticated electronic physician order-entry systems use clinical pathways as algorithms that have the ability to incorporate a variety of patient-specific factors (i.e., using "if-then" logic), such as risk factors for MDR pathogens, to better guide antimicrobial therapy selection. Antimicrobial agents of choice can also be programmed for certain target pathogens based on local susceptibility patterns. This technology helps incorporate guideline-recommended therapy while also providing a more tailored, patient-specific approach. It is important to note that these systems do not preclude the need for adequate follow-up and assessment of clinical response to therapy.

Interdisciplinary Relationships and Education

Steps should be taken to strengthen relationships between clinicians and AMS teams to promote collaboration in the decision-making process for antimicrobial use. Qualitative evidence from various studies indicates that the behavioral norms of prescribers as well as their attitudes should be considered before implementing interventions to help increase effectiveness of the change (Charani 2011). Open discussions as well as observation of respective work processes should be the initial steps in establishing collaboration between ID and ICU services.

Educational presentations—ideally at interdepartmental conferences—can facilitate a means for this education and discussion. Once productive interactions have been initiated, a needs assessment can be performed for various different units (e.g., medical ICU, surgical ICU, trauma ICU), and collaborative interventions should be tailored accordingly. These initial efforts of collaboration are perhaps even more important in the critical care setting because this domain often functions autonomously and many clinician-established relationships exist.

A recent survey conducted at three different Australian university teaching hospitals indicated that 100% of ICU medical staff agree that prudent antimicrobial use is important to reduce antimicrobial resistance in the critical care setting (Chaves 2014a). These results suggest a perceived need for AMS in the ICU even before engaging clinicians in AMS discussions. Time constraints have been identified as one of the most significant barriers to implementation of AMS principles for ICU clinicians; therefore, it is critical for efforts to be feasibly integrated into existing workflow processes (Chaves 2014a).

Collaboration between ID consultation services and intensive care clinicians in the ICU has been shown in various analyses to significantly decrease antimicrobial use (Peto 2008). In addition, ID consultation has been found to be independently associated with lower mortality (18% vs. 39%, p<0.01) in patients with critical illnesses such as candidemia (Patel 2005).

ANTIMICROBIAL TREATMENT PRINCIPLES

Successful prediction of a patient's infecting pathogen is the most important initial treatment consideration for critically ill individuals. Significant debate exists regarding which method provides the best predictive value of microbial etiology. Considerations before implementing treatment regimens

include typical bacterial pathogens for disease states, local susceptibility patterns and antibiogram data, and risk stratification for MDR organisms (Cotta 2014). Unfortunately, a highly reliable and predictive method has remained elusive to date because of significant overlap of patient risk factors for MDR pathogens and the complexity of accurately interpreting health care exposure.

Once antimicrobial therapy is initiated, optimization of regimens is important for patient outcomes and for prevention of downstream resistance. Implementing regimens with mindfulness of escalation or de-escalation and of pharmacokinetic/pharmacodynamic dosing characteristics can significantly influence treatment outcomes. Furthermore, defining the therapy duration can help limit unnecessary antimicrobial exposure.

Initial Selection of Antimicrobial Regimen

The initial use of inadequate antimicrobial therapy in medical and surgical ICUs has been described as an independent risk factor for mortality and carries up to a 5-times greater risk of hospital mortality (Kollef 1999). Therefore, timely and appropriate initial antimicrobial therapy is essential for positive treatment outcomes in the ICU setting. Initial choice of antimicrobial treatment regimens should be evidence-based, using the primary literature as well as IDSA guideline recommendations for common ICU infections such as hospital-acquired pneumonia (HAP) and sepsis etiologies.

An alternative approach includes examining the role of surveillance cultures in improving initial antimicrobial therapy. Here, antimicrobial regimens are directed to only cover pathogens found to be colonizing the individual patient in comparison with typical broad-spectrum therapy. Narrow spectrum therapy is implemented when surveillance cultures are negative. A study retrospectively investigated a hypothetical treatment algorithm based on routine respiratory surveillance cultures 2 to 5 days before treatment for HAP in the ICU. This investigation predicted that similar rates of antimicrobial appropriateness (87.6% vs. 88.5) would be achieved with surveillance culture-based algorithms compared with standard therapy (De Bus 2014). As expected, significantly less broad-spectrum antimicrobial exposure was observed. Because further trials are needed to adequately assess the role of surveillance cultures for antimicrobial initiation in the ICU, this approach is neither commonly used nor recommended at this time.

Local Susceptibility Patterns and Antibiogram Guidance

Antibiograms are often used in the inpatient setting to help identify local susceptibility (and resistance) patterns, as well as assist selection of empiric antimicrobial therapy. Antibiograms serve as a collective report of antimicrobial susceptibility data generated from microbiologic testing of clinical isolates. An antibiogram can be individualized for specific critical care areas. ICU-specific antibiograms should be provided whenever resources are available to ensure accuracy of information within the specific patient population. Significant differences in susceptibility rates have been described when comparing unit-specific and hospital-wide antibiograms (Binkley 2006). Trends in antimicrobial use should be correlated with antibiogram susceptibility and should be reviewed regularly to assess opportunities for improvement.

The Clinical Laboratory Standards Institute (CLSI) publishes guideline recommendations for antibiogram development and presentation. These recommendations are intended to enhance the accuracy and clinical utility of the antibiogram. The most recent update includes five primary recommendations (Box 2-1). A recent study that assessed 47 university hospitals for compliance with these recommendations revealed compliance rates ranging from 64% to 98% and noted that pharmacist involvement was critical in developing and reporting the antibiograms (Xu 2012).

A common pitfall observed for antibiograms that are reported frequently (e.g., quarterly) and are unit-specific (e.g., medical ICU) is that certain bug-drug combinations do not meet the 30-isolate minimum for testing, yet are still reported. This approach can be potentially dangerous because it increases the likelihood of either overestimation or underestimation of antimicrobial susceptibility. To reduce this error, the institution's microbiology laboratory should suppress sensitivity reports on antibiograms when fewer than 30 isolates are available.

Innovative and clinically useful combination antibiograms have also been described in the literature to tackle the issue of shared or cumulative resistance between different antimicrobial agents (Beardsley 2006). Although traditional antibiograms can individually depict antimicrobial agents with the best chance of covering a pathogen, a combination

Box 2-1. CLSI Recommendations for Antibiograms

1. Antibiogram documents should be prepared at least annually.
2. Only the first isolate of multiple identical isolates encountered for a patient should be reported in cumulative antibiograms.
3. Surveillance cultures should be excluded from antibiogram data.
4. All drugs tested that are appropriate for the organism species should be reported, and supplemental testing of drugs on resistant isolates should be excluded.
5. The cumulative antibiogram should include only organisms with at least 30 isolates tested.

Information from Clinical and Laboratory Standards Institute (CLSI). Analysis and presentation of cumulative antimicrobial susceptibility test data: approved guideline, 3rd ed. CLSI document M39-A3. Wayne, PA;2009.

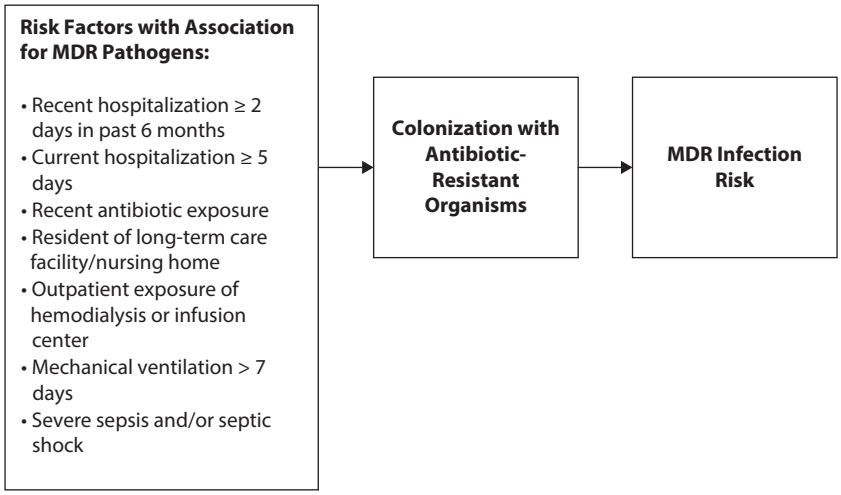

Figure 2-2. Aggregate risk factors for colonization with multi-drug-resistant (MDR) pathogens that increase the risk of infection in the critical care setting.

antibiogram can describe susceptibility rates with multiple (two or more) agents. For example, a combination antibiogram could show that, during a given period, *P. aeruginosa* isolates in an ICU are 94% susceptible to a combination of piperacillin/tazobactam and tobramycin, whereas a classically reported antibiogram might report these same *P. aeruginosa* susceptibilities as piperacillin/tazobactam (84%) and tobramycin (67%). Therefore, clinicians are armed with better information to select options with the greatest likelihood for antimicrobial success.

Of note, susceptibility profiles of key microbial pathogens may display both inter- and intra-hospital variability. Another study described that a different combination regimen was needed at the author's institution to provide optimal anti-pseudomonal coverage in the medical ICU (e.g., antipseudomonal β-lactam plus amikacin) versus the surgical ICU (e.g., antipseudomonal β-lactam plus levofloxacin) (Pogue 2011).

Double-Coverage of Gram-Negative Pathogens

Treatment guidelines for HAP/ventilator-associated pneumonia (VAP) indicate that a combination of an agent covering methicillin-resistant *Staphylococcus aureus* and two agents to cover a possible MDR gram-negative pathogen (typically an antipseudomonal β-lactam agent plus either an aminoglycoside or fluoroquinolone) should be considered in patients with late-onset HAP/VAP (ATS 2005). However, the optimal approach for empiric antimicrobial therapy remains controversial. The rationale for initiation of multiple agents for double coverage is to minimize the potential for inappropriate treatment. Identification of patients with risk factors for MDR pathogens is a key component in assessing the need of double coverage. Figure 2-2 depicts collective risk factors for MDR pathogens that have been described in the ICU setting; these serve as potential indicators for double coverage of gram-negative pathogens.

In a retrospective cohort study that analyzed the outcomes of empiric antimicrobial therapy choice in severe sepsis and septic shock, the addition of combination therapy against gram-negative pathogens could have increased appropriate empiric therapy rates by about 5% (Micek 2010). However, it is important to note that double coverage of antimicrobials has not always shown a treatment or mortality benefit in clinical studies. A large, multicenter randomized trial reported similar treatment outcomes and 28-day mortality rates with meropenem plus ciprofloxacin combination therapy versus meropenem monotherapy (RR 1.05; 95% CI, 0.78–1.42; p=0.74) (Heyland 2008). Furthermore, in an observational trial, ICU patients treated following clinical guidelines for nosocomial pneumonia with double coverage of gram-negative pathogens had a higher mortality rate that patients receiving monotherapy (79% vs. 65%, p=0.004) (Kett 2011). The authors deduced that the toxic effects of double antimicrobial therapy may have contributed to the heightened mortality rates.

Interpretation of Drug Allergy

Antimicrobial drug allergies can introduce a significant challenge for initiation of antimicrobial therapy. Although β-lactam antimicrobials are among the most reliable in the ICU and exhibit a fairly low toxicity profile, up to 20% of patients admitted to the hospital claim to have a penicillin allergy (Lee 2000). In comparison, only about 10% of patients who report an allergy are found to have penicillin hypersensitivity (Sogn 1992). Meanwhile, allergy documentation information, including allergy severity, is often absent

in medical records. Patients should be properly assessed for the presence and description of allergies to multiple β-lactam agents because allergic response to multiple agents has been shown to increase the likelihood of an allergic reaction to a subsequent β-lactam agent.

Traditional teaching has been that an allergic cross-reactivity rate of 10% or less is expected when alternative β-lactams are used in patients with a penicillin allergy. This belief has led to avoidance of β-lactams such as cephalosporins and carbapenems in patients reporting penicillin allergies, sometimes in mild cases of allergy. Contrary to this practice, recent literature suggests that overall β-lactam cross-reactivity is about 1% with third- and fourth-generation cephalosporins that exhibit dissimilar structural side chains (Campagna 2012). Furthermore, penicillin cross-reactivity rates are similarly low for carbapenems (Frumin 2009). These percentages of cross-reactivity in patients with penicillin allergy approach those described with the monobactam aztreonam (<1%), which is used readily in the presence of severe or anaphylactic penicillin allergy. A limitation of aztreonam is that it exhibits less overall antimicrobial coverage of *P. aeruginosa* than other antipseudomonal β-lactam agents.

These data indicate that a mild (e.g., not anaphylactic) penicillin allergy should not preclude use of alternative antipseudomonal β-lactams in the ICU. Tools such as penicillin skin testing have been performed in the ICU setting to help guide this therapy choice. A prospective, observational study of patients admitted to the ICU found that 88.5% of those reporting a penicillin allergy tested negative on penicillin skin testing. These test results helped change 81.5% of patient therapy to a β-lactam antimicrobial (Arroliga 2003). Unfortunately, a lack of personnel and resources to administer these time-intensive penicillin skin tests are often a key limiting factor for their clinical usefulness in the inpatient setting.

Time to Appropriate Antimicrobial Therapy

The ESKAPE pathogens (*Enterococcus faecium, S. aureus,* extended-spectrum β-lactamase-producing *Klebsiella pneumonia/Escherichia coli, P. aeruginosa, Acinetobacter baumannii,* and *Enterobacter* spp.) are particularly monitored and assessed because of their ability to "escape" many antibacterial agents by exhibiting significant drug resistance (Boucher 2009). As a result, significant delays in time to appropriate therapy for these ESKAPE pathogens have been described.

Delays in appropriate therapy in the ICU are detrimental to patient outcomes. Perhaps the most critical example of this is with escalating mortality that been observed with each 1-hour delay of appropriate antimicrobial therapy in critically ill patients with severe sepsis and septic shock. In one report, each hour that adequate antimicrobial administration was delayed in patients with septic shock reduced survival rates by 7.6% (Kumar 2006). For this reason, the updated Surviving Sepsis Campaign guidelines recommend intravenous antimicrobial therapy with activity against likely pathogens be administered within the first hour of recognition of sepsis and septic shock to optimize patient outcomes (Dellinger 2013).

Time to appropriate therapy and its effect on mortality has also been described for the treatment of candidemia in the ICU. Mortality risk increased by nearly 10% for each additional day without appropriate antifungal treatment with fluconazole (Garey 2006). Fungal isolates such as *Candida spp.* display significant incubation periods before positive culture results, necessitating prompt initiation of therapy as soon as preliminary culture findings are reported. Although pre-emptive therapy for clinical suspicion of fungal disease before culture results has been suggested, concerns for overtreatment and the inability to predict systemic candidiasis have precluded therapy in most circumstances unless high clinical suspicion is noted.

Pharmacokinetic/Pharmacodynamic Dose Optimization

The best microbiological predictor of treatment success for bacterial pathogens is the MIC of the organism. Investigations conducted in vitro, using animal models or mathematical patient simulations, and a limited number of human studies indicate that optimizing exposure of antimicrobials above the MIC of a pathogen (i.e., achieving a pharmacodynamic target) is associated with higher rates of bacterial eradication, treatment success, and lower mortality in critically ill individuals. Pharmacodynamic optimization of time-dependent antimicrobials occurs when free drug concentrations are maintained above the MIC (fT>MIC) of the target organism (about 50% of the dosing interval), whereas concentration-dependent antimicrobials such as aminoglycosides optimize bacterial killing with higher peak levels. Although β-lactam antibiotics exhibit exclusive time-dependent activity, nearly all other antibiotic classes utilize the area under the serum concentration curve/MIC ratio to establish different targets for gram-positive and gram-negative pathogens.

Extended or Continuous Infusion Antimicrobials

A retrospective study evaluated the clinical impact of extended-interval piperacillin/tazobactam in critically ill patients with *P. aeruginosa* infections. Patients with APACHE II scores of 17 or higher who received extended-infusion piperacillin/tazobactam, compared with the standard intermittent infusion, had a significantly lower 14-day mortality rate (12.2% vs. 31.6%, p=0.04) and shorter median duration of hospital stay (21 days vs. 38 days, p=0.02) (Lodise 2007). In a recent study, similar outcomes were observed with extended-infusion cefepime in the inpatient setting. Overall mortality, with greater than 50% of patients in each treatment group being treated in the ICU, was found to be significantly lower (3% vs. 20% days p=0.04) in the extended-infusion cefepime group versus the standard standard-infusion group when implemented for

the treatment of *P. aeruginosa* bacteremia and/or pneumonia. Median length of stay for patients in ICU was also found to be significantly less (8 vs. 8.5 days p=0.04) in the extended-infusion cefepime group (Bauer 2013).

In a prospective, observational study in a single institution's medical, surgical, and neurotrauma ICUs, extended infusion β-lactam use was compared with a historical control group receiving intermittent infusions for treatment of VAP (Nicasio 2010). Before implementation, an analysis was performed of local pathogen MIC distributions that applied pharmacodynamic modeling (targets of 50% fT>MIC for cefepime and piperacillin/ tazobactam and 40% fT>MIC for meropenem) to design regimens that would best achieve target attainment collectively within the ICU units. The regimen of extended-infusion cefepime or meropenem plus tobramycin and vancomycin exhibited the greatest probability of empiric VAP coverage and was administered in the study period. Both infection-related mortality (8.5% vs. 21.6%; p=0.029) and infection-related length of stay (11.7 ± 8.1 days vs. 26.1 ± 18.5 days; p<0.001) were significantly reduced for patients treated with this extended infusion regimen (Nicasio 2010).

Although continuous infusions of β-lactam antimicrobials enable consistent target attainment and therapeutic levels similar to (and sometimes exceeding) those with extended-infusion antimicrobials, the clinical benefits of continuous infusions have not been shown to be superior. In addition, continuous infusions require continuous line access, which increases the likelihood of drug compatibility issues. When concurrent line access is not available, particularly in ICU patients receiving multiple medications, additional percutaneous access is needed, which poses a risk of infection. For these reasons, continuous infusions are used primarily in patients with adequate line access for antimicrobials as well as other concomitant medications.

Dose Escalation

Many antimicrobials used in the ICU were approved on the basis of early studies conducted before advanced understanding of the agents' pharmacokinetic/pharmacodynamic parameters. Follow-up studies enhancing antimicrobial pharmacodynamic profiles and drug exposures have shown benefit in the critical care population. In addition to these factors, critically ill patients require different dosing approaches than non-critically ill patients. Of note, critically ill patients develop large volumes of distribution and enhanced drug clearance. In the absence of renal dysfunction, antimicrobial dosing should be escalated and optimized to account for these patient factors in critically ill individuals.

A recent report describes a clear relationship between antimicrobial concentrations obtained by dosing principles and patient outcomes in the ICU. In a prospective, multinational study of various β-lactam antimicrobial agents used in 384 critically ill adult patients, patients who did not achieve target attainment (50 % fT>MIC) were 32% more likely to have their antimicrobial therapy fail (OR 0.68; 95% CI, 0.52–0.91; p=0.009) (Roberts 2014). Furthermore, 16% of patients in this study did not meet this critical pharmacodynamic target for β-lactams, indicating that dose escalation may be necessary in nearly one of five critically ill patients.

Antimicrobial Therapy De-escalation

The core principle of de-escalation or streamlining therapy centers on the ability to reduce broad-spectrum antimicrobial consumption rates without compromising outcomes and, in most circumstances, with enhancing clinical outcomes. De-escalation opportunities should be particularly explored in patients receiving multiple agents. Antimicrobial de-escalation is often synonymous with selection of a narrow- and targeted-spectrum single agent. Currently, primary literature data do not support combination therapy for definitive treatment, fundamentally because of the lack of additional clinical benefit.

Although microbiologic culture findings typically return within 48–72 hours of submission, prompt de-escalation after clinical and microbiologic review has been shown to reduce broad-spectrum antimicrobial use in the ICU (Eachempati 2009) as well as total duration of antimicrobial therapy (Mokart 2014). Historically, clinicians have been concerned that de-escalation may have a negative impact on treatment outcomes and mortality. Recent data indicate that benefits of de-escalation on reducing antimicrobial consumption can be achieved without adversely affecting mortality (Eachempati 2009), whereas further studies have suggested a mortality benefit with de-escalation of HAP treatment in the ICU (2.3% vs. 10.8%, p=0.08) (Joung 2011).

Duration of Therapy

Duration of therapy is an important factor in AMS because colonization and infection with drug-resistant pathogens have been described with unnecessarily prolonged antimicrobial duration. Barriers to implementing appropriate duration of therapy are often experienced when certain minimal standards for executing treatment plans are not adequately assessed or communicated. These standards, which are integral to assessing appropriateness and should be documented within the medical record, include the treatment indication, the antimicrobial start date, and duration of therapy (Chaves 2014b). Although education can be helpful for teaching the importance of therapy duration, clinical pharmacists must play an active role to incorporate target treatment duration into disease state protocols as well as clinical documentation routines.

Similar to interventions described in daily audit initiatives, systematic follow-up is key for facilitating appropriate antimicrobial treatment end points. Combining minimum standards documentation with follow-up fosters the implementation of more concrete treatment plans. Daily guideline

reassessments in patients with VAP are associated with shorter duration of therapy (6.0 vs. 8.0 days, p=0.0001) (Micek 2004), and day 3 reassessments have also reduced mean antimicrobial duration in ICU patients with pulmonary infiltrates and suspicion of pneumonia (3 days vs. 9.8 days, p=0.0001) (Singh 2000). Furthermore, the use of a pharmacist-led antimicrobial documentation bundle to document and assess these minimum standards, along with daily follow-up in the ICU, has been shown to reduce median duration of echinocandin antifungal therapy (4.0 days vs. 2.0 days, p=0.001) (Guarascio 2013).

MICROBIOLOGICAL TOOLS FOR ANTIMICROBIAL STEWARDSHIP

Microbiological tools for the enhancement of AMS focus on the principles of timeliness of antimicrobial administration as well as predicting infectious etiology. Use of these tools can help to decrease time to appropriate antimicrobial therapy as well as to describe cases for which antimicrobials are not necessary.

Rapid Diagnostic Testing

The role of rapid diagnostic testing methods in AMS hinges on providing effective means for implementing appropriate antimicrobial therapy earlier in the disease process. De-escalation of therapy is principally dependent on microbiologic identification and susceptibility results; however, these results often take 48–72 hours with conventional culture methods (Figure 2-3). Advanced molecular testing techniques (e.g., polymerase chain reaction) deliver more timely microbiologic findings because results can be reported in as little as 1 hour or less. General characteristics of commercially available rapid diagnostic tests are summarized in Table 2-2.

These rapid diagnostic tests alone do not provide specific drug susceptibilities and must ultimately be run on an antimicrobial susceptibility testing platform. However, susceptibility profiles of certain organisms can sometimes be inferred by genetic identification (i.e., penicillin-binding protein 2a identification for methicillin-resistant *S. aureus*), and drug therapy decisions can often occur at the time of rapid diagnostic test result. Likewise, prompt de-escalation or discontinuation of therapy can lead to both improved short-term patient outcomes as well as long-term reductions in antimicrobial use and lower antimicrobial selective pressure.

Biomarkers to Guide Antimicrobial Treatment Decisions

Biomarkers such as WBC; C-reactive protein (CRP); and, most recently, procalcitonin (PCT), have been used as indicators for the presence or absence of infection in ICU patients, particularly for conditions such as sepsis and HAP/VAP. Differentiating infection from a simple inflammatory process is the main goal of clinically useful biomarkers. Clinical data show some promise for using biomarkers to make better-informed decisions for early, appropriate antimicrobial therapy, as well as prompt discontinuation of therapy that is not clinically indicated. As a result, integration of these biomarkers into the characterization and definition of ID states in the ICU setting have accelerated over the past few decades.

Although the potential of these biomarkers is substantial, limitations have been noted in clinical studies that may affect their overall clinical utility. Most consensus opinions regarding biomarker use note that antimicrobial therapy decisions should not be based exclusively on biomarker levels. Rather, these levels are a piece of the puzzle (in addition to clinical context and patient-specific variables) to assist the decision-making processes.

Procalcitonin

The biomarker PCT is a precursor of calcitonin, the production of which is elevated in response to systemic inflammation. Elevations are particularly observed in the presence of bacterial infections, although this relationship is not exclusive. Levels rapidly become detectable in the bloodstream in the presence of infection (within 2–4 hours), with peaks occurring within 24–48 hours. The rise in PCT corresponds with the level of inflammation present; more severe presentations of disease states usually correlate with pronounced PCT

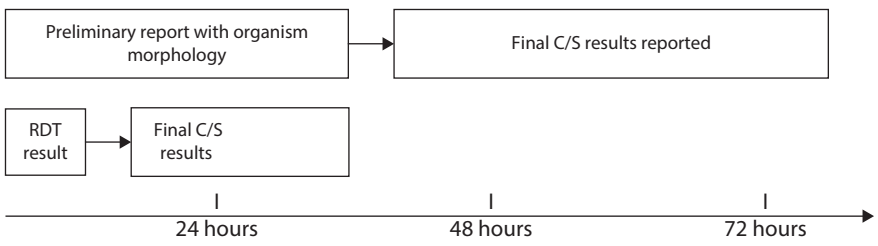

Figure 2-3. Average timeline for conventional bacterial culture and susceptibility methods versus rapid detection methods following initial culture growth

C/S = culture and susceptibility; RDT = rapid diagnostic test result.

Table 2-2. Features of Common Rapid Diagnostic Tests

Test	Detection method	Time to result (hours)	Advantages	Disadvantages
Culture colony test	Detection of specific gene expression	0.1–0.5	Ease of use, lowest cost, do not have to purchase specific testing platform	Few available assays and limited utility, organism-specific testing only
PCR	Detection of organism-specific DNA sequences	1–2	Ease of use	High cost, most only detect one group of bacterial or fungal species at a time
PNA-FISH	Hybridization to organism-specific RNA	0.5–2	Ease of use	High cost, only detect one group of bacterial or fungal species at a time
MALDI-TOF	Mass spectrometry	0.5–1	Ease of use, detects many bacterial and fungal species in one step	Highest cost

MALDI-TOF = matrix assisted laser desorption ionization-time of flight; PCR = polymerase chain reaction; PNA-FISH = peptide nucleic acid fluorescence in situ hybridization.

elevations. Box 2-2 indicates thresholds used for likelihood of potential bacterial infection in lower respiratory tract infections and sepsis (Schuetz 2011).

Daily PCT-guided therapy for the treatment of sepsis and VAP has been studied as both a diagnostic and prognostic tool in the ICU setting. Initiation and continuation of therapy is suggested at higher PCT levels and discouraged at lower concentrations. Although PCT has not proved helpful at reducing the initiation of antimicrobials in ICU patients, it has been found to safely reduce antimicrobial duration (effect sizes, 19.5%–38% reduction) (Agarwal 2011). The Surviving Sepsis Campaign guidelines currently assign a grade 2C recommendation for using low PCT levels or other biomarkers to guide discontinuation of antibiotics in patients who initially presented with sepsis but later have no evidence of infection (Dellinger 2013). Controversy still exists regarding the impact of PCT-guided therapy on ICU length of stay, and the use of this protocol has not been shown to significantly influence clinical outcomes or mortality rates.

Although many studies have described the clinical utility of PCT as an indicator of severe systemic infection, others have not fully elucidated its role in the ICU given its various limitations. Perhaps of most concern is the inability of PCT to differentiate between infectious and noninfectious disease processes. Surgery, trauma, burns, cardiac arrest, renal dysfunction, and certain malignancies all can elevate PCT levels in clinical circumstances. Furthermore, pooled analyses have indicated limited reliability with the diagnostic performance in sepsis (sensitivity 77%, specificity 79%) (Prkno 2013).

Box 2-2. Proposed Procalcitonin Level Thresholds for Clinical Significance in Lower Respiratory Tract Infections and Sepsis[a]

Normal level: < 0.1 ng/mL; antibiotics strongly discouraged

Suspected lower respiratory tract infection:

- 0.1 to < 0.25 ng/mL: low likelihood of bacterial infection; antibiotics discouraged
- ≥ 0.25 ng/mL: increased likelihood of bacterial infection; antibiotics encouraged

Suspected sepsis:

- 0.1 to < 0.5 ng/mL: low likelihood for sepsis; antibiotics discouraged
- ≥ 0.5 ng/mL: increased likelihood sepsis; antibiotics encouraged

[a]Consider initiation of antibiotics in all patients with a high suspicion of infection and clinically unstable patients regardless of the procalcitonin level.

C-Reactive Protein

The hepatic acute-phase reactant CRP is also used as a highly sensitive biomarker of inflammation. Unfortunately, a number of limitations exist for this use of CRP compared with PCT. Detection of CRP in the blood is possible about 12–24 hours after an inflammatory event, with peak levels obtained at about 48 hours; this indicates slower detection and peaks than PCT (Becker 2008). This protein also appears to be less specific for infection than PCT, and positive values are not as predictive of infection. Lastly, CRP can be affected by other comorbidities and anti-inflammatory drugs, further limiting its diagnostic utility. For this reason, CRP has a limited role as a marker of infection in ICU patients and is used less often than PCT to guide antimicrobial therapy.

SURVEILLANCE OF ANTIMICROBIAL USE AND DRUG RESISTANCE

Measuring antimicrobial use in the health care setting is recommended to better understand relationships between drug use and antimicrobial resistance. It is often one of the first AMS initiatives implemented; nevertheless, process changes and improved clinical outcomes are key drivers of long-term reductions in antimicrobial drug use. Antimicrobial use measurements are often performed at baseline before AMS initiatives, and longitudinal measures thereafter can help identify antimicrobial use trends after AMS implementation. Antimicrobial metrics can be measured on both the institutional and regional level, as well as benchmarked for national and international use.

Metrics of Antimicrobial Use

Two principal metrics have been applied to quantify antimicrobial use: defined daily dose (DDD) and days of therapy (DOT). The World Health Organization (WHO) recommends the metric of DDD and standardizes daily maintenance doses of antimicrobial agents for their main indication in adults. Recommended doses are for a 70-kg individual, and general maintenance doses are used to establish DDD metrics. To report figures in DDD units (g/day), the total grams of antimicrobial administered are summed for a given period, then divided by the WHO-assigned DDD. Table 2-3 depicts WHO-assigned DDD for empiric antimicrobial agents commonly used in the ICU.

Although DDD methodology provides users with a globally standardized metric, its inherent limitation is the potential for incorrect reflection of antimicrobial use if discrepancies exist between typical dosing patterns and the WHO-assigned DDD. Examples of these deviations include weight extremes that differ from normal body weight, dose adjustments in patients with end organ failure, and use of alternative dosing regimens that may differ from DDD defined values. Underestimation of common doses for many antimicrobial agents can occur, particularly in the ICU setting. Furthermore, these DDD metrics do not take extended-infusion antimicrobial regimens into account; therefore, administration of one fewer dose per day of an antimicrobial (e.g., extended-infusion piperacillin/tazobactam regimens) can significantly affect these DDD metrics.

In contrast, the DOT defines one day of therapy as administration of a single agent at any dose or dosage strength. Measuring DOT bypasses the patient specific limitations of DDD but can overestimate drug use because any number of doses administered on a given day is assigned one DOT. Despite this limitation, it has been proposed that DOT may be a more accurate measure of drug utilization in a critical care population because of the higher doses initiated in comparison with non-critically ill patients. In addition to discrepancies with standardized DDDs, the frequent need for dose adjustments in patients with renal insufficiency suggest DOT may be more precise in the ICU population (Zagorski 2002).

When an institution measures both DDD and DOT, comparability between the two measures is inconsistent. Nevertheless, AMS programs may choose to measure both DDD and DOT to provide more robust data trend analyses when each are individually compared with historical figures. Also, if an institution intends to change the metric it currently uses, it is prudent to first measure both for a number of years until another proper baseline of data is established. The most accurate way to report DDD and DOT is in figures standardized per 1000 patient-days; this serves as a standardized way to account for hospital occupancy and census changes over time. It is unknown at this time whether DDD or DOT measures are more predictive of antimicrobial resistance rates.

Table 2-3. Defined Daily Doses (DDD) and Equivalent Intravenous Antimicrobial Dosage Regimens

Antimicrobial Agent	DDD (g)	Intravenous Equivalent Regimen
Vancomycin	2	1000 mg every 12 hours
Linezolid	1.2	600 mg every 12 hours
Cefepime	2	1000 mg every 12 hours
Piperacillin/tazobactam	14	None, in between the following: 3.375 g every 6 hours (12 g/day piperacillin component) and 4.5 g every 6 hours (16 g/day)
Imipenem/cilastatin	2	500 mg every 6 hours
Meropenem	2	500 mg every 6 hours
Gentamicin, tobramycin	0.24	Various, weight-based
Amikacin	1	Various, weight-based
Ciprofloxacin	0.5	250 mg every 12 hours
Levofloxacin	0.5	500 mg every 24 hours

Patient Care Scenario

A 45-year-old man (weight 92 kg) is diagnosed with VAP and initiated on the following antimicrobial regimen: vancomycin 1500 mg intravenous every 12 hours, plus piperacillin 3.375 g intravenous every 8 hours (extended-infusion), plus tobramycin 450 mg intravenous every 24 hours. A causative pathogen is not found on culture results; therefore all three empiric antimicrobials are continued for a total 7-day treatment course. The AMS committee has asked for an estimation of the antimicrobial use in this patient for an ongoing antimicrobial use study in the ICU. Assuming that the patient received all scheduled doses for each day of therapy, calculate drug utilization in both DDD and DOT measurements for the patient's regimen.

ANSWER

The first step is to add the patient's total daily dose for each antimicrobial agent. Next, DDD standard units should be obtained from the WHO DDD website. Then, divide the patient's total daily dose for each agent by the applicable WHO DDD unit. For example, this patient has a total daily dose of vancomycin of 3 g (therefore, 3 g ÷ 2 g DDD unit = 1.5 DDDs). Days of therapy should be calculated based solely on whether a patient was administered a dose of antimicrobial on a particular day. Therefore, the patient will be calculated as receiving 1 DOT per day the antimicrobial is administered. The following table depicts the antimicrobial metric measures observed in this patient:

Antimicrobial Agent	Doses/Day	Total Daily Dose	WHO DDD Unit (g)	DDD Measure	DOT Measure
Vancomycin	2	3000 mg (3g)	2	1.5	1
Piperacillin/Tazobactam	3	9000 mg (9g)	12	0.75	1
Tobramycin	1	450 mg (0.45g)	0.24	1.9	1
Total	6	N/A	N/A	4.15	3

Total DDD = 4.15 DDD x 7 days = 29.05 DDD.
Total DOT = 3 DOT x 7 days = 21 DOT.

N/A = not available.

1. World Health Organization. Collaborating Centre for Drug Statistics Methodology. ATC/DDD Index 2015. Oslo, Norway: WHO; 2013.
2. Polk RE, Fox C, Mahoney A, et al. Measurement of adult antibacterial drug use in 130 U.S. hospitals: Comparison of defined daily dose and days of therapy. Clin Infect Dis 2007;44:664-70.

Trends in Drug Resistance

Surveillance and reporting of trends in antimicrobial resistance can be difficult because of inconsistencies in microbiologic methodologies and in the data reporting processes. For example, changes in microbiologic testing methods, as well as reference breakpoints should be considered. Any changes in microbiologic testing platforms (e.g., in manufacturer, in automated susceptibility testing) or in susceptibility breakpoint values by the CLSI (which occur frequently) should be further investigated. Divergence in these processes can have either positive or negative effects on antimicrobial resistance rates. Communication between critical care and AMS services can help to ensure that significant microbiologic changes have not been made when resistance changes are observed.

The most common way to find resistance prevalence trends in the ICU for a specific period is through the use of antibiogram data. However, how often these data are reported (i.e., yearly, quarterly, monthly) may greatly influence observations of short-term versus long-term trends in resistance. Using data from antibiograms that report more tested isolates over longer periods (e.g., yearly antibiogram data) can show more sustained resistance trends. In addition, resistance trends should be correlated with antimicrobial consumption methods. If antimicrobial metrics indicate significant use of antimicrobial(s) correlating with higher resistance rates, ICU unit-specific metric analyses can be performed in collaboration with AMS practitioners to further evaluate such trends and potential sources. Once a precipitating factor is suspected, the most effective means for behavioral or procedural change is to encourage discussion with all key stakeholders, with particular focus on inclusion of ID and critical care practitioners.

ANTIMICROBIAL STEWARDSHIP OUTCOMES

Positive outcomes resulting from implementation of AMS in the ICU require a dedicated AMS service working in collaboration with critical care pharmacists and other ICU practitioners. Favorable outcomes are highly dependent on

both active intervention and regular follow-up. Regardless of factors such as the level of institutional sophistication and implementation of rapid diagnostics, surveillance software, and clinical pathway development, a clinical practitioner with AMS knowledge must perform active AMS intervention to produce robust and sustained outcomes. Many studies document positive stewardship outcomes in the ICU setting. It is worth noting that most of these data are from uncontrolled, before-and-after observational trials in single-center ICUs; therefore, study outcomes should be interpreted according to the quality of evidence reported.

Clinical Outcomes and Mortality

Most published studies of AMS interventions are associated with a decrease in antimicrobial use, and sustained reductions in antimicrobial use may positively influence antimicrobial resistance trends over time. Because antimicrobial-resistant infections contribute to increases in hospital length of stay and mortality, positive changes in local ecology can improve these end points. These studies are hard to perform over long periods, and it is very difficult to describe a specific association of these end points with stewardship interventions. Therefore, many AMS studies are limited in their focus and primarily report on patient outcomes from currently implemented interventions. Nonetheless, various studies adopting AMS implementation coupled with optimization of therapy have reported several hard-to-measure outcomes such as reductions in length of stay and patient mortality.

Antimicrobial Costs

The monetary benefits of AMS initiatives have been well documented in the literature, and the IDSA guidelines suggest that funding for AMS programs can be self-sustaining because of these monetary benefits (Dellit 2007). A reduction in antimicrobial costs is a downstream pharmacoeconomic benefit of appropriate antimicrobial use. Implementation of effective AMS programs will provide an immediate impact on annual antimicrobial savings. These cost reductions tend to narrow over time simply because increases in nationwide antimicrobial resistance necessitates the use of newer, more expensive antimicrobials. It is important to note that cost should never be a precluding factor for appropriate therapy, because the treatment costs for recurrent or relapsing disease greatly exceed those of the upfront medication costs. Furthermore, institutions should view AMS as a quality-improvement initiative rather than an exclusive cost-savings initiative because appropriate treatment decisions may not always be the most cost-effective options.

A culmination of study data predicts that AMS programs initiated in the ICU can lead to attributable cost savings of about $5–10 (U.S.) per ICU patient day (Kaki 2011). Limited data exist for indirect cost savings resulting from AMS interventions (e.g., reduction in antimicrobial resistance rates, avoidance of adverse effects) because these indirect cost savings are notoriously difficult to quantify. In addition, establishing relationships and causality between these indirect data and stewardship interventions is challenging. Furthermore, many cost analyses also do not take into account personnel costs of implementing AMS, which can be significant depending on the type of AMS model implemented at a particular institution.

CONCLUSION

Antimicrobial stewardship measures have been shown to be productive in the ICU setting. Prevention of indiscriminate antimicrobial use is the responsibility of ID/AMS clinicians as well

Practice Points

Performing AMS in the ICU setting can be challenging. Antimicrobial stewardship guidelines and primary literature describing stewardship interventions in the ICU provide these general principles:

- **Prospective audit with intervention and feedback and formulary restriction are hallmark antimicrobial stewardship principles, upon which other stewardship processes can be built.**
- **Interdisciplinary relationships and collaboration between ID/AMS and critical care practitioners can enhance treatment outcomes as well as stewardship intervention success.**
- **Choice of empiric antimicrobial therapy for critically ill patients is based on a variety of principles, including common infectious etiologies of the disease state, risk factors for MDR pathogens, local susceptibility patterns, and antibiogram guidance.**
- **A significant emphasis should be placed on providing early, appropriate therapy for patients in the ICU because delays of even 1 hour in patients with septic shock have been shown to significantly increase mortality rates.**
- **Pharmacokinetic/pharmacodynamic optimization of antimicrobial treatment regimens in the ICU have been shown to positively influence treatment outcomes as well as mortality in patients who are critically ill.**
- **Patients should be assessed for possible antimicrobial therapy de-escalation and discontinuation upon availability of the culture result because this approach has been shown to significantly decrease antimicrobial exposure in ICU patients.**
- **Biomarkers, such as PCT, can be used clinically to factor into the decision-making process for both treatment and discontinuation of antimicrobial therapy for potential infection. Biomarkers should not be used exclusively to make antimicrobial therapy decisions.**
- **Antimicrobial utilization is often measured in either DDD or DOT, and provides an estimate of total antimicrobial use over time in comparison with antimicrobial resistance rates.**
- **Antimicrobial stewardship has been shown to effectively lower antimicrobial use and duration, and clinical benefits regarding patient length of stay and mortality should indirectly follow from the protective effect of lower antimicrobial resistance rates.**

as critical care pharmacists and practitioners. Collaboration between these clinician groups has shown synergies for patient outcomes and promotes a sense of accountability for overall AMS success. Core interventions such as prospective audit with intervention and feedback and formulary restriction are of utmost importance and should serve as the backbone of AMS implementation. A bundle approach of multiple stewardship strategies with evidence for effectiveness will likely produce the most significant results in the ICU. Despite the lack of robust study data regarding AMS outcomes in the ICU, stewardship initiatives have largely shown benefit while not causing harm or adverse patient outcomes. Ideally, future studies evaluating the benefit of AMS in the critical care setting will involve large, randomized controlled studies.

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Self-Assessment Questions

21. The antimicrobial stewardship (AMS) committee at your hospital has begun an institution-wide rollout to disseminate AMS responsibilities to decentralized pharmacists. As the critical care specialist, you are responsible for stewardship initiatives in the ICUs. Which one of the following would be the most effective initial strategy to implement in coordination with the AMS committee?

    A. Antimicrobial cycling to reduce resistance rates
    B. Combination antimicrobial therapy to prevent resistance development
    C. Antimicrobial order forms requiring order justification to decrease antimicrobial use
    D. Prospective audit with intervention and feedback to decrease antimicrobial use

22. The AMS committee has notified your department that meropenem utilization and resistance has increased in recent months. As a result, they would like to implement an efficient process for daily, prospective audit of meropenem use in a 22-bed medical ICU each morning before patient care rounds. Which one of the following would be the most appropriate means for implementation?

    A. Using computerized surveillance software
    B. Individual review of each electronic patient profile
    C. Staff pharmacist phone notification after meropenem medication orders
    D. A meropenem antibiotic stewardship form placed in the medical chart

Questions 23 and 24 pertain to the following case.

The ICU medical director at TopHealth Hospital has decided to implement AMS within the medical and surgical/trauma ICUs. The AMS committee has agreed to be a collaborative resource for this initiative.

23. Administrators of TopHealth Hospital decide that a prior authorization process is needed because of high antimicrobial utilization. Which one of the following would be the best first step to ensure the essential principles of a prior authorization process are implemented?

    A. Perform prospective audits of orders using surveillance software
    B. Communicate with AMS service for order approval
    C. Document order rationale in the medical record
    D. Integrate restriction criteria into computerized physician order-entry systems

24. Which one of the following is the most effective initial approach to communicate this AMS initiative at TopHealth Hospital?

    A. Educational presentations at medical resident conferences
    B. Departmental discussion of specific needs and barriers
    C. A letter to prescribers indicating AMS process
    D. Electronic dissemination of AMS process in website platform

25. An ICU at a small, rural hospital has been charged with implementing AMS services. Because of limited resources, which one of the following would have the greatest likelihood of producing consistent AMS outcomes?

    A. Longitudinal monitoring of antibiotic prescribing trends
    B. Active intervention with regular and consistent follow-up
    C. Antibiogram reporting
    D. Providing education at clinical conferences

Questions 26–30 pertain to the following case.

A.T. is a 75-year-old man recently transferred to the medical ICU for HAP. He was admitted to the hospital 7 days ago from his residence, a nursing home facility. A family member reports that A.T. had a pneumonia episode 1 month before hospitalization. Bronchoalveolar lavage is performed, and cultures reveal gram-negative rods, with identification and susceptibilities pending. Antibiogram susceptibilities for *Pseudomonas aeruginosa* in the medical ICU over the past year reveal the following: piperacillin/tazobactam: 79%; cefepime: 82%; meropenem: 91%; tobramycin 67%; ciprofloxacin 42%. Additional combination antibiogram report below:

***Pseudomonas aeruginosa* susceptibility using combination agents**

	Piperacillin/ tazobactam	Cefepime	Meropenem
Tobramycin	88%	91%	97%
Ciprofloxacin	83%	86%	94%

26. Which one of the following would be the most appropriate initial regimen for A.T.?

    A. Piperacillin/tazobactam plus ciprofloxacin
    B. Tobramycin
    C. Cefepime plus tobramycin
    D. Piperacillin/tazobactam

27. The ICU attending physician asks you to administer the antipseudomonal β-lactam agent chosen for A.T.'s treatment regimen as an extended infusion. Which one of the following is most likely to result from this choice for A.T.?

    A. Shorter duration of therapy needed
    B. Longer hospital length of stay
    C. Less chance of pharmacodynamic target attainment
    D. Reduction in mortality

28. Assuming a high suspicion for *P. aeruginosa* pneumonia, and in the absence of finalized culture results, which one of the following provides the most valuable information for choosing A.T.'s initial antimicrobial coverage?

    A. Prior history of pneumonia
    B. Combination antibiogram findings
    C. Risk for multi-drug resistant pathogens
    D. IDSA guideline recommendations

29. The AMS pharmacist pages you after being alerted that cultures have finalized for A.T. on day 3, revealing *E. coli* susceptible to ceftriaxone. So far, A.T. has made only modest improvements in his breathing status. Which one of the following is best to recommend for A.T.?

    A. De-escalate therapy to ceftriaxone
    B. Convert parenteral cefpodoxime to oral
    C. Change to ceftriaxone plus tobramycin
    D. Escalate therapy to a carbapenem

30. Which of the following would be most likely to pose a threat to the validity of the antibiogram data used to guide treatment for A.T.?

    A. Surveillance culture results excluded from the data
    B. Supplemental testing of drugs on resistant isolates included in the data
    C. Repeat isolates obtained from the same patient excluded from the data
    D. An organism with 45 isolates tested included in the data

31. A 36-year-old man is admitted to the medical ICU for septic shock. Antimicrobial orders for continuous infusion piperacillin/tazobactam and ciprofloxacin are placed immediately. The orders are filled and administration begins within 1 hour of placing the order. As a result of acute kidney injury, the piperacillin/tazobactam and ciprofloxacin doses are modified 6 hours later. Which one of the following will have the greatest effect on this patient's likelihood of survival?

    A. Time to appropriate therapy
    B. Administration of continuous infusion piperacillin/tazobactam
    C. Combination antimicrobial therapy
    D. Dose optimization

32. A 42-year-old woman with VAP is on your service in the surgical ICU. She has a history of penicillin allergy with a documented rash in the electronic medical record. Which one of the following antipseudomonal therapies is best to recommend for this patient?

    A. Aztreonam
    B. Ciprofloxacin
    C. Cefepime
    D. Piperacillin/tazobactam

33. A 56-year-old man is admitted to the medical ICU with a drug-resistant *Pseudomonas aeruginosa* bloodstream infection. The patient currently has a peripheral intravenous line as well as a peripherally inserted central catheter. Various other scheduled intravenous drugs are being administered. The ICU service initiates intermittent infusion cefepime 2 g every 8 hours (CrCl 92 mL/minute). You are asked to help optimize drug pharmacokinetics/pharmacodynamics because the MIC is 4 mcg/mL. Which one of the following is best to recommend for this patient?

    A. Change to continuous infusion cefepime.
    B. Double the current dose.
    C. Change to extended infusion cefepime.
    D. Extend the dosing interval.

34. You are the critical care pharmacist in charge of the care and AMS of all patients in a hospital medical and surgical ICU. An attending physician approaches you regarding possible ways to prevent inappropriately long durations of antimicrobial therapy. You currently have limited time and resources and are unable to provide daily reassessments of antimicrobial therapy for all patients. Which one of the following schedules for reassessing patients on antimicrobials would be the most productive and efficient use of your time?

    A. Every other day
    B. Weekly on Mondays, Wednesdays, and Fridays
    C. 72 hours after initiation of therapy
    D. 24 hours after initiation of therapy

35. A patient is being evaluated for suspected sepsis in the medical ICU and has been initiated on broad-spectrum antimicrobial therapy with vancomycin plus cefepime. Preliminary blood culture results reveal gram-positive cocci in 1 out of 2 blood culture bottles. The patient's procalcitonin (PCT) level is 0.52 ng/mL. Which one of the following is best to recommend for this patient?

    A. Continue broad-spectrum antimicrobial therapy until culture results finalize.
    B. Continue broad-spectrum antimicrobial therapy until PCT is below 0.4 ng/mL.
    C. Discontinue broad-spectrum antimicrobial therapy.
    D. De-escalate broad-spectrum antimicrobial therapy.

36. A 55-year-old man is admitted to the medical ICU after acute myocardial infarction and cardiac arrest. His C-reactive protein (CRP) level is significantly elevated. Blood cultures are drawn, although the team currently finds no other signs of infection. Which one of the following is best to recommend for this patient?

    A. Initiate broad-spectrum antibacterial agents.
    B. Initiate empiric antifungal therapy.
    C. Withhold antimicrobials pending repeat CRP level.
    D. Withhold antimicrobials unless infectious source verified.

37. A 74-year-old man is admitted to the medical ICU with severe sepsis. He has a medical history of extended-spectrum β-lactamase producing *E. coli* infection from a decubitus ulcer. Intravenous vancomycin and meropenem are initiated, and blood cultures with use of rapid MALDI-TOF testing reveal an *E.coli* bloodstream infection. Which one of the following is best to recommend for this patient?

    A. Continue meropenem and reassess once antimicrobial susceptibilities return.
    B. Continue meropenem for the duration of treatment.
    C. De-escalate therapy to ceftriaxone.
    D. Change therapy to cefepime.

38. Your ICU medical director asks you to investigate specific rapid diagnostic testing methods for faster differentiation between methicillin-resistant and methicillin-sensitive *Staphylococcus aureus* bloodstream infections. The unit estimates about 1–3 cases of staphylococcal bloodstream infections per month and has limited resources to cover the costs of diagnostic testing. Which one of the following options would best serve this purpose?

    A. Culture colony test
    B. PCR
    C. PNA FISH
    D. MALDI-TOF

39. The AMS team at your institution, in collaboration with the critical care department, is assessing longitudinal measures of antimicrobial consumption. Your hospital has a large ICU bed capacity and census as well as an extensive nephrology service because of the management of many end-stage renal disease patients. Which one of the following would yield the most accurate yearly measure of antimicrobial consumption?

    A. Absolute DOT metrics
    B. DOT/1000 patient days
    C. Absolute DDD metrics
    D. DDD/1000 patient days

40. For the past 5 years your institution has been using DDD measurements as a baseline for antimicrobial consumption. The critical care department has decided to use DOT metrics moving forward. Which one of the following would be best for the institution to measure?

    A. DDD and DOT for 3 years, then exclusive DOT
    B. DOT exclusively moving forward
    C. DOT after 5 more years of baseline DDD
    D. DOT and DDD on alternating years

41. You have scheduled a meeting with the inpatient pharmacy manager to discuss ICU antimicrobial drug costs for the previous year. Daily prospective audit with clinician feedback in the ICU has been implemented for 5 years, and substantial progress has been made in decreasing overall antimicrobial consumption and improving ICU antimicrobial susceptibility. Antimicrobial consumption metrics in DOT/1000 patient days reveal a fairly consistent decrease over this period. Recently, cost savings of antimicrobial use in the ICU have steadily declined, and expenses are only slightly below levels before AMS implementation. Which one of the following is best to recommend to the pharmacy manager?

    A. No significant changes are necessary.
    B. Plan to further restrict prescriptive authority of certain prescribers
    C. Change AMS interventions to prior authorization
    D. Change AMS personnel performing prospective audit processes

Learner Chapter Evaluation: Antimicrobial Stewardship in the ICU.

As you take the posttest for this chapter, also evaluate the material's quality and usefulness, as well as the achievement of learning objectives. Rate each item using this 5-point scale:

- Strongly agree
- Agree
- Neutral
- Disagree
- Strongly disagree

19. The content of the chapter met my educational needs.
20. The content of the chapter satisfied my expectations.
21. The author presented the chapter content effectively.
22. The content of the chapter was relevant to my practice and presented at the appropriate depth and scope.
23. The content of the chapter was objective and balanced.
24. The content of the chapter is free of bias, promotion, or advertisement of commercial products.
25. The content of the chapter was useful to me.
26. The teaching and learning methods used in the chapter were effective.
27. The active learning methods used in the chapter were effective.
28. The learning assessment activities used in the chapter were effective.
29. The chapter was effective overall.

Use the 5-point scale to indicate whether this chapter prepared you to accomplish the following learning objectives:

30. Analyze key antimicrobial stewardship (AMS) principles and determine how they can be applied in the ICU.
31. Design empiric antimicrobial treatment regimens for patients at risk of multidrug resistant pathogens and assess treatment courses for opportunities to optimize therapy.
32. Justify the use of rapid diagnostic technology for AMS and detect limitations for their use.
33. Distinguish differences between the clinical utility and characteristics of the biomarkers procalcitonin and C-reactive protein.
34. Evaluate antimicrobial therapy for a patient in both defined daily dose and days of therapy metrics and describe the role of antimicrobial consumption in drug resistance.
35. Please provide any specific comments related to any perceptions of bias, promotion, or advertisement of commercial products.
36. Please expand on any of your above responses, and/or provide any additional comments regarding this chapter:

Antibiotic Resistance in the ICU

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LEARNING OBJECTIVES

1. Analyze strategies for minimizing the development and spread of antibiotic resistance.
2. Evaluate the differences in mechanism of antibiotic resistance.
3. Develop a treatment plan for infections caused by resistant gram-positive organisms.
4. Compose an antimicrobial regimen for resistant gram-negative infections.

ABBREVIATIONS IN THIS CHAPTER

ESBL	Extended-spectrum β-lactamase
hVISA	Heterogeneous-resistant vancomycin-intermediate *Staphylococcus aureus*
KPC	*Klebsiella pneumoniae* carbapenemase
MDR	Multidrug resistant
MRSA	Methicillin-resistant *Staphylococcus aureus*
VAP	Ventilator-associated pneumonia
VISA	Vancomycin-intermediate *Staphylococcus aureus*
VRE	Vancomycin-resistant Enterococcus

INTRODUCTION

Patients admitted to the ICU have higher acuity of disease, both infectious and non-infectious, and a greater number of comorbidities (e.g., renal dysfunction, hepatic dysfunction and hemodynamics dysfunction) than ward patients. The association of appropriate empiric antibiotic use in the ICU with improved outcomes has been well described. The ICU population has the highest occurrence of nosocomial infections; these infections lead to increased morbidity, increased hospital costs, and decreased survival rates compared with a general ward population (Blot 2008; Vandijck 2008; Vincent 1995). The use of mechanical ventilators and the need for multiple indwelling devices for ICU patients are all risk factors for increased nosocomial infections.

The Extended Prevalence of Infection in Intensive Care (EPIC II trial) showed that 51% of ICU patients were classified as infected, and 71% of the patients were receiving antibiotic therapy (Vincent 2009). As a result, ICU patients have a higher use of antibiotics, which can result in the development and amplification of multidrug resistant (MDR) and even more resistant infections. The National Healthcare Safety Network found higher rates of antibiotic-resistant pathogens in ICU patients than in non-ICU patients (Sievert 2013). Studies examining the impact of gram-negative bacterial resistance on patient outcome showed that antibiotic resistance was associated with increased crude mortality rate, prolonged hospital length of stay, and increased cost (Shorr 2009).

Patients infected with resistant pathogens are more likely to experience a delay in receiving appropriate antibiotics, which results in higher mortality rates (Hyle 2005). In patients presenting with septic shock, each hour of delay in administering of appropriate antibiotics was associated with a 7.6% decrease in survival (Kumar 2006). A universally accepted definition of MDR—and even for extensively drug

resistant and pandrug resistant infections—is lacking. The European Centre for Disease Prevention and Control and the Centers for Disease Control and Prevention recently proposed these definitions:

- *Multi-drug resistant*—acquired non-susceptibility to at least one agent in three or more antimicrobial categories,
- *Extensively drug-resistant*—non-susceptibility to at least one agent in all but two or fewer antimicrobial categories (i.e., bacterial isolates remain susceptible to only one or two categories), and
- *Pandrug-resistant*—non-susceptibility to all agents in all antimicrobial categories (Magiorakos 2012).

Because of the higher rates of infections and higher rates of antibiotics resistance, the potential for initial inadequate antibiotic selection can be detrimental if clinicians are not vigilant. *Inadequate antibiotic use*, defined as the use of agents with lack of activity against the pathogen, has been associated with increased mortality, increased hospital and ICU length of stay, and increased cost to the health system (Cosgrove 2006; Garnacho-Montero 2003; Kollef 1999). The additional cost of MDR infections in hospitalized patients has been estimated at $6000 to $30,000 per patient and up to $55 billion per year within the United States (Cosgrove 2006, Smith 2013). When adjusted for disease severity, exposure time, underlying diseases, and other contributing factors, mortality was higher in patients with MDR infections compared with those with non-MDR infections. In addition, patients with MDR pathogens are more likely to receive more toxic and potentially less-effective antibiotic regimens.

BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:

- General knowledge of the pathophysiology of antibiotic resistance
- The consequence of inappropriate antibiotic management of ICU patients
- General knowledge of infection control procedures
- The various antibiotics used to treat infections caused by gram-positive and gram,-negative organisms

ADDITIONAL READINGS

The following free resources have additional background information on this topic:

- Alekshun MN, Levy SB. Molecular mechanism of antibacterial multidrug resistance. Cell 2007;128:1037-50.
- Arias CA, Murray BE. Antibiotic-resistant bugs in the 21st century – a clinical super challenge. N Engl J Med 2009;360:439-43.
- Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children. Clin Infect Dis 2011;52:285-92.
- Kanj SS, Kanafani ZA. Current concepts in antimicrobial therapy against resistant gram-negative organisms: extended-spectrum ß-lactamase-producing Enterobacteriaceae, carbapenem-resistant Enterobacteriaceae, and multidrug-resistant *Pseudomonas aeruginosa*. Mayo Clin Proc 2011;86:250-9.
- Siegel JD, Rhinehart E, Jackson M, et al. Management of multidrug-resistant organisms in health care settings, 2006. Am J Infect Control 2007;35:S165-93.

TRANSMISSION OF RESISTANT ISOLATES

Coined in 2008, the ESKAPE bugs, which include *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* spp., tend to cause the bulk of nosocomial infections and develop the major resistance to current available antibiotics (Rice 2008). A recent report from the National Healthcare Safety Network showed methicillin-resistant *S. aureus* (MRSA) rates as high as 55%, vancomycin-resistant Enterococcus (VRE) rates as high as 83%, carbapenem-resistant *Klebsiella* spp. as high as 13%, and MDR *P. aeruginosa* as high as 18% (Sievert 2013).

The increased prevalence of MDR, extensively drug resistant, and even pandrug resistant pathogens can be attributed to higher use of broad-spectrum antibiotics that result in induction, selection, introduction, and disseminations of resistant strains. Previous studies have shown the occurrence of collateral damage (selection of antibiotic-resistant organisms and the unwanted development of colonization or infection with such organisms) with the increased use of antibiotics, especially cephalosporins and fluoroquinolones.

Increased use of third-generation cephalosporins and fluoroquinolones has resulted in increased rates of VRE, MRSA, extended-spectrum β-lactamase (ESBL) and *Clostridium difficile* infections (Patterson 2004; Weber 2006). The increased resistance is observed especially among organisms such as *S. aureus*, *E. coli*, *P. aeruginosa*, *H. influenza*, *Enterococcus* spp., *S. pneumoniae* and *K. pneumoniae,* which are the most common organisms isolated from ICUs (Zhanel 2008). In examining rates of MDR within the National Healthcare Safety Network database, 10% of the *P. aeruginosa* isolates, 15% of the *K. pneumoniae* isolates and 60% of the *A. baumannii* isolates were resistant to at least three antibiotic classes (Kallen 2010). Increased hospital stay, duration of mechanical ventilation, and previous exposure to antibiotics are associated with an increased occurrence of antibiotic resistance (Hyllienmark 2012).

In examining rates of ESBL-producing versus non-ESBL *Klebsiella* spp., exposure to fluoroquinolones and β-lactam/

β-lactamase inhibitor combinations was associated with ESBL-producing *Klebsiella* spp. (Wener 2010). Prior treatment with fluoroquinolones or extended-spectrum cephalosporins, use of carbapenems, severity of illness, and admission to the ICU were all associated with the development of carbapenem-resistant *K. pneumonia* infections (Gasink 2009; Hussein 2009).

The Infectious Disease Society of America and American Thoracic Society guidelines for the management of health care-associated pneumonia described risk factors to help identify patients at risk of developing MDR pathogens. Risk factors include receipt of antibiotics within the preceding 90 days; current hospitalization of 5 or more days; presence of invasive devices such as endotracheal tubes and intravascular and urinary catheters; high frequency of antibiotic resistance within the community of the hospital unit; immunosuppression; and health care–associated pneumonia risk factors (i.e., hospitalization of 2 or more days within the preceding 90 days, residence in a nursing home or extended care facility, home infusion therapy, chronic dialysis within 30 days, home wound care, and family member with MDR pathogen) (ATS 2005). Prior antibiotic therapy, residence in a nursing home, and prior hospitalization were determined in the multivariate analysis to be independent predictors of MDR pathogen infection or colonization upon ICU admission (Nseir 2010).

Box 3-1. CDC Recommendations for Management of Multidrug Resistant Organisms in the Health Care Setting

- Administrative measures
  - Making infection prevention and control an organizational priority for patient safety
  - Identification and isolation of colonized patients
  - Implementation of systems to communicate information about reportable infections
  - Implementation of a multidisciplinary process to monitor and improve health care personnel adherence
- Education and training of health care personnel
- Judicious use of antimicrobial agents
  - Implementation of a system to review antimicrobial utilization and development of local antibiogram
  - Implementation of a system to provide clinicians with susceptibility reports and analysis of current trends
- Surveillance of microbiological results
- Infection control precautions
  - Standard and contact precautions
- Environmental measures
  - Environmental cleaning and disinfection
  - Equipment cleaning and disinfection

Information from: Siegel JD, Rhinehart E, Jackson M, et al. Management of multidrug-resistant organisms in health care settings, 2006. Am J Infect Control 2007;35:S165-93.

PREVENTION STRATEGIES

Education is vital because clinicians tend to believe that antibiotic resistance is more of a problem at the national level rather than at their local institution (Giblin 2004). The key barriers to fighting antibiotic resistance include instituting antibiotic control, the resistance of the tendency to treat colonization rather than true infections, and discontinuing antibiotic therapy after appropriate duration.

Infection control in the ICU has been an important tool in prevention of development of nosocomial infections, but it also has been a useful tool in the prevention in the development of antibiotic resistance. The CDC Healthcare Infection Control Practice Advisory Committee released evidence-based recommendations for the management of MDR organisms in the health care setting (Box 3-1).

Isolation precautions and hand hygiene are valuable in minimizing the spread of resistance. Transmission of MRSA and VRE is thought to occur through skin to skin/surface and aerosol transmission, especially in the presence of viral respiratory infections, frequent hand-nose contacts, and poor hand washing techniques by health care workers. Strategies for monitoring, compliance with hand hygiene, environmental cleaning, and adequate staffing has been efficacious in the control of MRSA and VRE, as well as the use of chlorhexidine to decrease rates of colonization (Lin 2010).

The use of dedicated instruments and equipment as well as the placement of colonized or infected patient in isolated rooms are effective strategies to prevent the transmission of these resistant organisms. Strategies such as limiting urinary catheter use for appropriate indications and shortening the duration of catheter use when possible, as well as the use of silver-coated catheters, have been efficacious strategies in limiting the rate of catheter-associated UTIs (Shuman 2010).

Use of appropriate laboratory methods for the detection of carbapenemase-producing Enterobacteriaceae is vital because these pathogens can remain unrecognized with routine culture and antibiotic susceptibility testing methods. New rapid molecular methods for organism identification can more quickly identify the pathogen and the resistance profile. These methods include the use of polymerase chain reaction (PCR), multiplex PCR, nucleic acid extraction and PCR amplification, peptide nucleic acid fluorescent in situ hybridization (PNA FISH), and matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) (Bauer 2014).

Various pharmacologic strategies have been used in the prevention of nosocomial infections. Use of pharmacologic agents can decrease the colony counts of bacteria flora that can potentially cause invasive infections, thus decreasing the rate of nosocomial infections. Chlorhexidine mouthwash and nasal mupirocin have been used to decrease the rates of ventilator-associated pneumonia (VAP) and MRSA infections. The use of selective digestive tract and oropharyngeal decontamination agents that have activity against gram-negative bacteria, yeasts, and *S. aureus* decreases mortality,

ICU-acquired bacteremia, and ICU and hospital stay (de Smet 2009). However, the uses of these decontamination strategies have been reported to result in outbreaks of ESBL-producing bacteria and colistin- and aminoglycoside-resistant Enterobacteriaceae (Halaby 2013; Al Naiemi 2006). This finding was not observed in studies examining the effect of the decontamination strategies on antibiotic resistance, other than increased rates of rectal carriage of aminoglycoside-resistant gram-negative bacteria in patients who received selective digestive tract decontamination (Oostdijk 2014; Daneman 2013).

In intubated patients, the use of topical polymyxin/tobramycin/amphotericin B in the oropharynx and via the gastric tube in addition to nasal mupirocin and chlorhexidine body wash resulted in lower infection rates, total acquired infections, VAP, and catheter-related bloodstream infections (Camus 2014). This decontamination regimen also resulted in a lower number of acquired infections caused by resistant Enterobacteriaceae and *P. aeruginosa*, and fewer patients acquired infections caused by MDR gram-negative bacilli. The use of chlorhexidine mouthwash, nasal mupirocin, and chlorhexidine body washes can be considered in all patients; however, further considerations need to be made regarding selective digestive or oropharyngeal decontamination based on the potential of resistance development.

In addition to infection prevention, the management of antibiotic resistance within the ICU can involve multiple strategies. These approaches include developing institutional treatment guidelines; selecting appropriate empirical antibiotics based on risk factors for antibiotic resistance as well as data from the local antibiogram; selecting appropriate duration of antibiotic use; de-escalating empirical antibiotic regimens when possible; using formulary restrictions of broad-spectrum antibiotic use; implementing a multidisciplinary antibiotic management program; and using pharmacokinetic and pharmacodynamic principles for antibiotic dose optimization (Gandhi 2010). The use of empiric broad-spectrum antimicrobial coverage in patients with risk factors for MDR pathogens should not be avoided as a strategy to provide appropriate empiric therapy. Diligence, however, must be exercised in monitoring microbiological cultures for opportunities to narrow coverage for isolated pathogens as a means to prevent inappropriately broad or long courses of antibiotics that further propagate resistance.

The development of institutional clinical treatment guidelines has been shown to improve rates of appropriate empiric antibiotic use, patient outcomes, and appropriate antibiotic use, as well as to potentially prevent the emergence of resistant pathogens. The use of clinical guideline protocols has been associated with higher rates of appropriate empiric antibiotic therapy, decreased antibiotic duration, and lower incidence of recurrence in treatment of VAP (Ibrahim 2001). The consideration of risk factors for MDR pathogens and local microbiological data when selecting antibiotics can improve patient outcomes. Strategies to decrease antibiotic use include both promoting appropriate duration and de-escalation of therapy.

The development of multidisciplinary teams to review and improve antibiotic use and improve patient care, and the formal formation of antimicrobial stewardship programs has been linked with improved patient outcome and decreased antibiotic exposure, emergence of MDR pathogens, and hospital cost. The term *antimicrobial stewardship* refers to coordinated interventions designed to improve and measure the appropriate use of antimicrobial agents by promoting the selection of the optimal antimicrobial drug regimen, including dosing, duration of therapy, and route of administration (SHEA 2012; Dellit 2007).

The use of combination empiric antibiotic therapy in select populations (i.e., severe sepsis/septic shock) with high severity of illness and/or risk factors for MDR pathogens has been shown to improve patient outcomes because it increases the probability of appropriate empiric antibiotic therapy; however, this strategy needs to be paired with an effective system for antibiotic de-escalation, because studies currently do not support the continued use of combination therapy for the treatment of susceptible pathogens for the prevention of emerging resistance, production of synergy, or development of additive antibiotic effect (Micek 2010).

The Society of Critical Care Medicine Surviving Sepsis Campaign guideline recommends 3–5 days of combination empiric antibiotic therapy before de-escalation if culture results are not available. Formulary restriction of broad-spectrum agents is a strategy that can be used to reduce overuse of the antibiotics leading to resistance. Prospective monitoring is required because formulary restriction of a specific antibiotic can result in the compensatory shift in the use of another antibiotic. Evidence currently does not support the use of antibiotic cycling in the prevention of the emergence of MDR pathogens (Warren 2004; Gruson 2003).

The impact of an antibiotic management program has been shown to be the management of outbreaks of MDR organisms. The use of pharmacokinetic and pharmacodynamic principles for dose optimization includes extended-interval aminoglycoside dosing, aggressive fluoroquinolone dosing, attainment of the appropriate vancomycin level for the infection, and continuous or prolonged infusion of β-lactams. The application of these principles has been efficacious in improving patient outcomes and may prevent development of MDR pathogens.

MECHANISM OF RESISTANCE

The mechanisms for the development of antibiotic resistance are thought to occur through three primary mechanisms: (1) alteration/acquisition of genetic materials, (2) development of an altered biochemical pathway, and (3) modification of antibiotic targets. Bacterial resistance to antibiotics can

Table 3-1. Mechanism of Antibiotic Resistance and Antibiotic Affected

Mechanism	Example	Antibiotics Affected
Altered PBP	PBP2	β-lactam
	mecA	β-lactam
Altered target	*vanA, vanB*	Vancomycin
	erm	Macrolides
	G2576U	Linezolid
	gyrA, parC	Fluoroquinolones
	rpoB	Rifampin
	tet	Tetracyclines
	mprF	Daptomycin
	Altered DHPS/DHFR	Sulfonamides/trimethoprim
Decreased uptake	Phosphotransferase	Aminoglycosides
	OprD	β-lactam
Efflux pump	*mef*	Macrolides
	MexAB-OprM	Fluoroquinolones, β-lactam
	AcrB-TolC	Fluoroquinolones, β-lactam, tetracyclines
	tet	Tetracyclines
Enzymatic degradation	Ambler class	β-lactam
Enzymatic modification	Adenyltransferase/acetyltransferase	Aminoglycosides
Innate	Phospholipid composition	Daptomycin
Chromosome mutation	*gyrA, parC*	Fluoroquinolones
Overproduction of target	Peptidoglycan	Glycopeptides
Transformation	PBP alteration	Penicillin

DHFR = dihydrofolate reductase; DHPS = dihydropteroate synthase; PBP = penicillin-binding protein.

Information from: Giedraitiene A, Vitkauskiene A, Naginiene R, et al. Antibiotic resistance mechanisms of clinically important bacteria. Medicina 2011;47:137–46; and Alekshun MN, Levy SB. Molecular mechanism of antibacterial multidrug resistance. Cell 2007;128:1037-50.

be intrinsic or it may be acquired through acquisition of exogenous genes, mutations of cellular genes, or a combination of the two. Acquisition of exogenous genes can occur by means of plasmids through conjugation or transformation, transposons through conjugation, and integrons and bacteriophages through transduction. Mutations of cellular genes through spontaneous mutations are rare but can occur by means of adaptive mutations during replication. Multiple mechanisms of resistance can result in the resistance to the same antibiotic (Table 3-1).

GRAM-POSITIVE ORGANISMS

Gram-positive organisms represent the infectious etiology of 45.6% of severe sepsis in the United States. The most common pathogens encountered are *S. aureus* (62.7%), *Streptococcus* spp. (22.6%), and *Enterococcus* spp. (4.3%), with MRSA being a significant predictor for mortality (Ani 2015). Both MRSA and VRE are important causes of catheter-related bloodstream infections, and MRSA is also a common cause of VAP.

Staphylococcus aureus

The most common cause of health care-associated infections is *S. aureus*, a gram-positive cocci that grows in clusters (Sievert 2013). It is a commensal organism that colonizes the skin and the nasopharynx; as a result, this organism is often implicated in bloodstream infections, pneumonia, and skin and soft-tissue infections. In the ICU, respiratory tract infection, especially pneumonia, represents the most common infection with the highest mortality (Angus 2001).

Although *S. pneumonia* is the most common cause of community-acquired pneumonia, MRSA is a common etiology for health care–associated pneumonia. Infections with MRSA remain one of the most important causes of hospital-associated bacterial infections. The EPIC II study showed up to 65% methicillin-resistance in *S. aureus* strains within the United States (Box 3-2) (Vincent 2009). The impact of MRSA was associated with increased length of hospital stay and hospital charges, as well as increased mortality risk (Cosgrove 2005; Reed 2005; Engemenn 2003).

Box 3-2. Risk Factors for Resistant Gram-Positive Infections

MRSA

- Previous stay in hospital or long-term care facilities
- ICU stay
- Intravascular devices
- Prior or prolonged antibiotic therapy
- Chronic underlying illness
- Surgical wounds
- Advanced age

VRE

- Highly immunocompromised patients
- Previous antibiotic exposure (mostly vancomycin, cephalosporins, and agents with anaerobic activity)
- Enteral feeding
- Comorbidities such as diabetes, renal failure, or hemodialysis
- Prolonged hospital stay

Information from: Clark NM, Hershberger E, Zervos MJ, et al. Antimicrobial resistance among gram-positive organisms in the intensive care unit. Curr Opin Crit Care 2003;9:403-12.

Penicillin resistance in *S. aureus* developed in the 1950s through the production of an inducible β-lactamase, leading in turn to the development of methicillin (also nafcillin and oxacillin), which are stable versus the β-lactamase. The development of methicillin resistance in the 1980s was the result of the expression of an altered penicillin-binding protein 2 (PBP2), which has a reduced affinity for β-lactams (Stryjewski 2014). Nosocomial-associated MRSA (mainly USA100 strain) is typically resistant to multiple classes of antibiotics, including β-lactams, macrolides, fluoroquinolones, and clindamycin. However, a recent strain of community-associated MRSA (USA300 strain) is commonly susceptible to clindamycin, fluoroquinolones, sulfamethoxazole/trimethoprim, and tetracyclines.

Vancomycin resistance (MIC ≥ 16 mcg/mL) was first reported in the 2000s, stemming from the transfer of *vanA* gene from *Enterococcus* spp. (Askari 2012; Tenover 2009). With increases in the *S. aureus* vancomycin MIC (4–8 mcg/mL) that do not reach the resistant threshold, vancomycin-intermediate *S. aureus* (VISA) is thought to occur through thickening of the peptidoglycan cell wall (van Hal 2011). Patients with vancomycin-susceptible infections who experience treatment failure can also be infected with heterogeneous-resistant VISA (hVISA), which is the occurrence of a subpopulation of vancomycin-resistant *S. aureus* within a colony of susceptible isolates and is associated with increased rates of treatment failure (Casapao 2013). Surveillance studies have reported the prevalence of hVISA to be 10%–43%, with higher frequencies in isolates with higher vancomycin MIC (Sader 2009).

Enterococcus spp.

The *Enterococcus* spp. are gram-positive cocci that grow in pairs or chains that are part of human normal flora and typically reside within the GI tract. They cause intra-abdominal infections, bacteremia, endocarditis, UTI, and wound infections. The EPIC II study showed vancomycin resistance rates of about 50%, with greater than 85% of the *Enterococcus faecium* also resistant to ampicillin and penicillin and greater than 50% resistant to gentamicin (see Box 3-2) (Vincent 2009; Clark 2003).

Vancomycin resistance was first reported in the 2000s, stemming from an alteration in the terminus on the peptidoglycan precursor (D-ala-D-lac, D-ala-D-ser instead of D-ala-D-ala), that confers reduced vancomycin binding. The alteration is characterized by six phenotypes, with *vanA* and *vanB* being the two most common, residing on plasmids that can be transferred to other organisms (e.g., *S. aureus*). Penicillin resistance is characterized by altered PBP binding, whereas aminoglycoside resistance is conferred by reduced cell wall permeability, ribosomal mutations, and the presence of aminoglycoside-modifying enzyme (Hollenbeck 2012). The isolation of *Enterococcus* spp. from peritoneal fluids in patients with severe infections was determined to be a predictor of mortality (Dupont 2011).

Treatment Strategies

Current treatment of MRSA often relies on the use of vancomycin as first-line therapy. This treatment strategy is currently being reconsidered with the emergence of vancomycin resistance (VISA and hVISA), as well as potential lower clinical efficacy rates when comparing vancomycin with other agents. Use of vancomycin or ampicillin for *Enterococcus* spp. can be considered for susceptible isolates, but as a result of the high rates of penicillin resistance (especially for *E. faecium*) and VRE, other agents should be considered for empiric therapy. Therapeutic drug monitoring for vancomycin is necessary because of the potential for nephrotoxicity with elevated trough levels and the potential for treatment failure with subtherapeutic trough levels.

Linezolid is an oxazolidinone approved for the treatment of nosocomial pneumonia, community-acquired pneumonia, complicated and uncomplicated skin and skin structure infections, and vancomycin-resistant *E. faecium* infections caused by susceptible organisms. Linezolid has been best studied in the treatment of *S. aureus* nosocomial pneumonia and in the treatment of MRSA skin and soft tissue infections. Use of linezolid has been considered for the empiric coverage of MRSA, especially in patients with acute renal failure. Linezolid has also been used for the treatment of *S. aureus* bacteremia and for the treatment of CNS infections based on its excellent CNS penetration. Linezolid has been used as empiric therapy in patients with previous or suspected VRE infections.

Considerations must be made when starting linezolid in a patient concurrently on serotoninergic agents (i.e., selective serotonin receptor antagonist, serotonin norepinephrine receptor antagonist, fentanyl, and amphetamines) because linezolid is a weak monoamine oxidase inhibitor and can lead

to serotonin syndrome. Major adverse effects to monitor include bone marrow toxicity, particularly thrombocytopenia, ocular neuropathy, and peripheral neuropathy. Benefits should outweigh the risk of neurotoxicity when using linezolid for a duration greater than 2 weeks.

Daptomycin is a lipopeptide approved for the treatment of complicated skin and skin structure infections and *S. aureus* bacteremia, including patients with right-sided infective endocarditis. Daptomycin has become a good alternate for the treatment of MRSA bacteremia as well as for the treatment of hVISA. High-dose (8–10 mg/kg) daptomycin has been recommended for the use in patients with persistent MRSA bacteremia associated with vancomycin failure and endocarditis based on potential higher daptomycin clearance in critically ill patents, resulting in lower AUC indexed to the MIC (Liu 2011; Falcone 2013). High-dose daptomycin has also reported to be efficacious in the treatment of MRSA meningitis (Riser 2010). Daptomycin has also been used as empiric therapy of patients with non-pneumonia VRE infections. Combination therapy of daptomycin with β-lactams (e.g., oxacillin, nafcillin, ceftaroline), linezolid, fosfomycin, rifampin, aminoglycosides, and sulfamethoxazole/trimethoprim has been used to treat difficult *S. aureus* and enterococcal infections, especially bacteremia and meningitis (Dhand 2014).

The "see-saw" effect (development of daptomycin resistance with concurrent decrease in β-lactams MIC) can be observed with the use of daptomycin for MRSA in combination with β-lactams (Yang 2010). Considerations must be made when starting daptomycin in a patient concurrently on a statin because of the increased risk of myopathy and rhabdomyolysis. The use of statins should be temporarily discontinued while the patient is receiving daptomycin. Daptomycin should not be used for the treatment of pneumonia because of the activity of pulmonary surfactants in inactivating daptomycin. Major adverse effects to monitor include myopathy, rhabdomyolysis, and eosinophilic pneumonia. Patients on daptomycin should have creatine kinase level monitored regularly, regardless of co-administration of a statin.

Ceftaroline is an advanced cephalosporin with activity versus MRSA and *E. faecalis* because of its affinity for binding to PBP2a and PBP2x. Ceftaroline is currently approved for the treatment of acute bacterial skin and skin structure infections and community-acquired bacterial pneumonia caused by susceptible organisms. Extensive experience is lacking for the use of ceftaroline for the treatment of MRSA bacteremia and nosocomial pneumonia; however, a case series suggests that ceftaroline can be used for the treatment of these conditions, especially with a regimen of higher-frequency dosing (every 8 hours) (Ho 2012). A study examining the use of ceftaroline for the treatment of *S. aureus* bacteremia has just been completed, and the results are pending. The manufacturer has submitted an application to the FDA for the treatment of MRSA bacteremia. The use of daptomycin in combination with ceftaroline as salvage therapy for MRSA bacteremia has been effective in providing clinical cure (Sakoulas 2014). Major adverse effects include the potential for hematologic toxicities (i.e., anemia and neutropenia) with prolonged courses.

Telavancin is a lipoglycopeptide with activity versus MRSA and susceptible *Enterococcus*. Telavancin is currently approved for complicated skin and soft structure infections and hospital-acquired pneumonia/VAP caused by susceptible organisms. Its use within the ICU is somewhat limited because of the potential toxicities and other available options. Caution should be exercised when starting telavancin in patients with prolonged QTc intervals or who are taking agents that can prolong QTc intervals. Telavancin can also result in artificially prolonged activated PTT, so concurrent use of intravenous heparin is contraindicated. Because of increased risks of mortality in patients pre-existing CrCl of 50 mL/min or less, and of fetal development toxicity in pregnant women, the use of telavancin is subjected to a risk evaluation and mitigation strategies (REMS) notification. Major adverse effects to monitor include nausea and vomiting and increased rates of nephrotoxicity.

GRAM-NEGATIVE ORGANISMS

Gram-negative organisms were responsible for 51.5% of the cases of severe sepsis in the United States over the past 20 years. The most common pathogens encountered are *E. coli*, *P. aeruginosa,* and *Klebsiella* spp. (Ani 2015). Risk factors associated with health care–associated infection caused by extensively drug resistant gram-negative organisms include immunocompromised state and use of amikacin, levofloxacin, or sulfamethoxazole/trimethoprim within the past 30 days (Patel 2014). Presence of VAP or prior use of colistin and carbapenem were associated with carbapenem-resistant gram-negative bacteremia (Routsi 2013).

The ESBL-producing Enterobacteriaceae spp. emerged after the introduction of cephalosporins. Risk factors for the development of ESBL include prior antibiotic use, ICU stay, indwelling devices, increased illness severity, prolonged hospitalization, emergency intra-abdominal surgery, mechanical ventilation, and nursing home residence (Pitout 2010). The re-administration of a previously administered antibiotic is associated with increased risk of resistance to that agent (El Amari 2001).

Classification for β-lactamases is typically based on the functional characteristic of the enzyme or protein sequence. Group 1 cephalosporinases are part of Ambler molecular class C that is present in many Enterobacteriaceae species, including *AmpC*-producing species (SPACE bugs), which include *Serratia* spp., *Pseudomonas aeruginosa*, *Acinetobacter*/ Indole positive Proteae (*Proteus*, *Morganella*, *Providencia* spp), *Citrobacter* spp., and *Enterobacter cloacae*. Group 2 serine β-lactamases include both Ambler molecular class A and D, taking in most of the traditional ESBL-producing species (*TEM, SHV, CTX-M*) and carbapenemase-producing species (*OXA,*

Table 3-2. Classification and Example of β-Lactamase Enzymes

Bush-Jacoby Group	Ambler Molecular Class	Substrate	Enzyme Type	Representative Enzyme	Common Organisms
1	C	Cephalosporin	*AmpC*	*AmpC*	*Enterobacter* spp., *Citrobacter* spp., *Morganella morganii*, *Pseudomonas aeruginosa*, *Serratia marcescens*
2a	A	Penicillin	ESBL (serine β-lactamases)	*PCI*	*Escherichia coli*, *Klebsiella* spp., *Proteus* spp., *Pseudomonas aeruginosa*
2b		Penicillin		*TEM-1, TEM-2, SHV-1*	
2be		ES cephalosporin		*TEMs, SHVs, CTX-Ms*	
2c		Carbenicillin		*PSE-2, CARB-3*	
2e		ES cephalosporin		*CepA*	
2f		Carbapenem		*KPC-2, IMI-1*	
2d	D	Carbapenem	Carbapenemase	*OXA-23, OXA-48*	*Acinetobacter baumannii*, Enterobacteriaceae, *Pseudomonas aeruginosa*
3a	B	Carbapenem	Metallo β-lactamases	*IMP-1, VIM-1, NDM-1*	*Acinetobacter baumannii*, Enterobacteriaceae, *Pseudomonas aeruginosa*
3b		Carbapenem		*CpthA*	

Information from: Bush K, Jacoby GA. Updated Functional Classification of β-lactamases. Antimicrobial. Agents Chemother 2010;54:969-76; and Hall BG, Barlow M. Revised Ambler classification of β-lactamases. J Antimicrobial Chemother 2005;55:1050-1.

KPC [K. pneumoniae carbapenemase]), as well as gram-positive β-lactamases (*PCI*). Group 3 metallo β-lactamases are part of Ambler molecular class B, which includes carbapenemases (*IMP, VIM, NDM*) (Table 3-2).

Enterobacteriaceae

Enterobacteriaceae are gram-negative bacilli that cause a wide range of infections, including cystitis, pneumonia, catheter related infection, and intra-abdominal infections. The most common organisms are *K. pneumoniae, E. coli*, and *Enterobacter* spp.; these pathogens can produce ESBLs, especially in patients with prolonged hospital stays or invasive medical devices. In patients with intra-abdominal infections, up to 13% of *K. pneumoniae* and 10% of *E. coli* are ESBL-producing isolates (Hawser 2013). Carbapenem-resistant Enterobacteriaceae was found in 4% of bloodstream infections and 5% of pneumonia. In addition, the presence of MDR *Klebsiella* spp. was observed in 16% of UTIs and 13% of VAPs (Zilberberg 2013). Production of *K. pneumoniae* carbapenemase, or *KPC*, is especially problematic because it results in decreased susceptibility to virtually all β-lactam antibiotics, as well as resistance to other antibiotics. The ESBLs are plasmid-mediated, and their potential for transfer makes effective control and treatment difficult.

Treatment of resistant Enterobacteriaceae is often dependent on the specific antibiotic susceptibility for the specific pathogen. Use of a cephalosporin as empiric therapy would not be reliable for suspected serious ESBL-producing infections. Cefotaxime and ceftriaxone are less susceptible to hydrolysis by ESBL than ceftazidime, but none of these agents are recommended as empiric therapy for suspected ESBL-producing organisms. Ambler class A ESBL-producing strains (e.g., *E. coli*, *Klebsiella* spp., *Proteus* spp.) are potentially susceptible to cephamycins (cefoxitin and cefotetan); however, resistance can develop during therapy in the presence of efflux pumps (Martinez-Martinez 1999). Bacteria strains (e.g., *Enterobacter* spp, *Serratia* spp.) that produce *AmpC* β-lactamases (Ambler class C) are resistant to cephamycins and to β-lactam/β-lactamase inhibitor combinations, but they remain susceptible to cefepime. The use of β-lactam/β-lactamase inhibitor combinations (specifically piperacillin/tazobactam and, to some extent, ticarcillin/clavulanate) for ESBL is a potential option based on the tazobactam and clavulanate activity versus Ambler class A ESBLs. These antibiotics may, however, be susceptible to the inoculum effect, in which the MIC increases with increased number of organisms (Peterson 2008).

Carbapenems are one of the first-line agents for serious infections caused by ESBL-producing Enterobacteriaceae except

for carbapenemase-producing strains. Fluoroquinolones, sulfamethoxazole/trimethoprim, fosfomycin, and nitrofurantoin may also be used if the isolates are susceptible and infections sites are appropriate for the antibiotic based on clinical indication (i.e., nitrofurantoin for cystitis). Treatment options for carbapenemase-resistant organisms include colistin, tigecycline, minocycline, and aminoglycosides, based on the susceptibility results, as well as aztreonam in metallo-β-lactamase producing strains. The use of aminoglycoside monotherapy is not recommended because of poor clinical outcomes, especially in severe systemic infections, and the rapid development of resistance.

High-dose tigecycline (200-mg loading dose followed by 100 mg twice daily) has been used in patients with infections caused by MDR bacteria, but recent studies have indicated a potential for increased mortality (Cheng 2015; De Pascale 2014; Sbrana 2013). The use of combination therapy with at least two agents with in vitro activity (typically a combination of tigecycline, colistin, and aminoglycoside, and even meropenem) had mortality benefit in the treatment of *KPC* and in carbapenemase-producing Enterobacteriaceae when compared with monotherapy (Tumbarello 2012; Falagas 2014).

Pseudomonas aeruginosa

P. aeruginosa is a non-lactose fermenting gram-negative bacilli that is associated with UTIs, bloodstream infections, pneumonias, surgical site infections, and burn site infections. Multidrug resistant *P. aeruginosa* isolates were found in 15% of bloodstream infections and 22% of pneumonia in all hospitalized patients; 21.9% of the bloodstream infections and a similar proportion of pneumonia cases were found to have originated in the ICU (Zilberberg 2013).

In addition to the expression of β-lactamases, *P. aeruginosa* can also express mutations in DNA gyrase and aminoglycoside-modifying enzymes, as well as decrease the expressions of porins, increase number of efflux pumps, and express modification in outer membrane permeability (Lister 2009). Treatment of *P. aeruginosa* infection is often difficult because of its intrinsic resistance to multiple antibiotics. Rates of resistance are dependent on geographic regions and tend to be higher in large teaching hospitals and in patients with previous antibiotic usage (Harris 2002).

The best empiric agents for *P. aeruginosa* are cefepime, ceftazidime, anti-Pseudomonal carbapenems, piperacillin/tazobactam, fluoroquinolone, and aminoglycosides. Initial therapy with a β-lactam and either aminoglycoside or fluoroquinolone combination may be warranted to ensure initial adequate coverage. Similar to the treatment of infections caused by Enterobacteriaceae, monotherapy with aminoglycosides results in poor clinical outcomes, especially in severe systemic infections, and should not be considered in treatment of *Pseudomonas* infections. Use of colistin may be warranted in patients with carbapenemase-producing isolates.

Acinetobacter spp.

Acinetobacter spp. are aerobic gram-negative coccobacilli that cause opportunistic infections (e.g., pneumonia, soft-tissue infections, catheter-related infections, UTI) in critically ill patients. Risk factors for acquiring *Acinetobacter* spp. include tracheostomy, endotracheal intubation, ICU residence, prolonged mechanical ventilation, invasive procedures or devices, and recent use of antibiotics (Garcia-Garmendia 2001).

Treatment of nosocomial *Acinetobacter* spp. is difficult because isolates are typically resistant to cephalosporins, penicillins, and aminoglycosides. Resistant *Acinetobacter* spp can express efflux pumps, porin modifications, target site modifications, and β-lactamases. Use of a carbapenem is typically warranted if the organism is susceptible, and many experts recommend the concurrent use of an aminoglycoside (Urban 2003). Because sulbactam possesses the greatest intrinsic bactericidal activity versus *Acinetobacter* spp. among all β-lactamase inhibitors, the use of ampicillin/sulbactam may be considered for susceptible infections. Use of colistin (polymyxin E) or polymyxin B and tigecycline may be warranted for MDR *A. baumannii* if there is a lack of alternative options, although an in vivo study in a mouse model suggests that colistin may have the weakest antibacterial effect of all antibiotics tested (Montero 2002).

Stenotrophomonas maltophilia

Stenotrophomonas maltophilia is a non-lactose fermenting gram-negative bacilli that is a rare cause of opportunistic infections in critically ill patients who have received broad-spectrum antibiotics (especially carbapenems, extended-spectrum cephalosporins, and fluoroquinolones). Risk factors for colonization or infection include tracheostomies, ICU residence, mechanical ventilation, use of broad-spectrum antibiotics, serious comorbidities, organ transplantation, hematologic malignancies, neutropenia, chemotherapy, use of corticosteroids, and use of central venous catheters, with the presence of prosthetic devices being associated with colonization (Dinani 2003). The presence of *S. maltophilia* often represents colonization; therefore, the clinician should consider the necessity of treatment with antibiotics. Treatment of *S. maltophilia* often requires the use of a non-β-lactam because it is intrinsically resistant to most β-lactam antibiotics (Looney 2009). Sulfamethoxazole/trimethoprim remains the most active antibiotic with more than 90% in vitro susceptibility and is the agent of choice for *S. maltophilia* (Gales 2001; Looney 2009). Of the β-lactam agents, ticarcillin/clavulanate is the most active agent, with ceftazidime being an alternate agent; however, resistance to ticarcillin/clavulanate is noted in up to 60% of the cases. Of the fluoroquinolone class, moxifloxacin has the most potent activity, with up to 85% of tested isolates being sensitive. Consideration can also be made for the use of minocycline and tigecycline in the treatment of resistant strains.

DOSING CONSIDERATIONS

Patients in the ICU have altered pharmacokinetic parameters because of altered absorption (altered perfusion), distribution (altered volume of distribution), metabolism (altered hepatic blood flow), and excretion (altered renal function); this presents challenges in achieving adequate dosing of antibiotics in this population (Smith 2012). Consideration should also be given to the potential for drug toxicities, the presence of renal and hepatic failures, the presumed site of infections, and the ability of antibiotics to achieve adequate levels at the site of infection. Aggressive dosing is often required to ensure adequate concentrations are achieved (Roberts 2009).

Antibiotics such as β-lactams (e.g., cefepime, carbapenems, piperacillin/tazobactam, aztreonam) and vancomycin are characterized as time-dependent antibiotics. Antibiotic such as aminoglycosides and fluoroquinolones are characterized as concentration-dependent antibiotics. Use of continuous or extended infusion for time-dependent antibiotics (e.g., β-lactams, vancomycin) and extended-interval aminoglycosides and high-dose fluoroquinolones have been promoted to improve bacterial eradication and improve patient outcome. Extended infusion of antibiotics have included dosing schemes such as 4-hour infusions of meropenem 500 mg, doripenem 500 mg, and piperacillin/tazobactam 4.5 g. Daily continuous infusion of cefepime 4 g, ceftazidime 4 g, imipenem/cilastatin 2 g, meropenem 4 g, piperacillin/tazobactam 18 g, and vancomycin 30 mg/kg have also been described. The use of continuous or extended infusion of

Patient Care Scenario

A 62-year-old man (height 69", weight 92 kg) is admitted from a nursing facility to the ICU for acute abdominal pain after a recent colectomy. His WBC is 17.2 x 10^3 cells/mm^3, heart rate is 122 beats/minute, blood pressure is 87/55 mm Hg, and temperature is 101.1°F (38.4°C). He has a history of heart failure, hypertension, stroke, chronic kidney disease (SCr 2.5 mg/dL), and diverticulosis. One month ago, he was admitted to the hospital and was found to have acute diverticulitis. During that admission, he underwent a total colectomy. After surgery and being stabilized on the hospital floor, he was transferred to a long-term acute care facility to complete 14 days of intravenous ceftriaxone and metronidazole. Although all cultures during the hospitalization were negative, he had an elevated WBC and a fever in the first 3–4 days after surgery. While at the nursing facility, he completed his intravenous antibiotics and was progressing well. His home drugs before this admission included aspirin 325 mg orally daily, furosemide 20 mg orally twice daily, carvedilol 12.5 mg orally twice daily, lisinopril 10 mg orally daily, and pravastatin 20 mg nightly. The patient is admitted from the ED with signs of septic shock. He is given one dose of piperacillin/tazobactam and vancomycin and started on intravenous fluids and norepinephrine. A CT scan reveals a leakage of the end anastomosis of the colectomy, and the patient is emergently taken for surgical treatment. Blood cultures are taken before the administration of antibiotics. After surgery, he is transferred to the surgical ICU and continued on piperacillin/tazobactam and vancomycin. The next day, the preliminary blood culture reveals abundant *Escherichia coli.* During rounds, the medical team asks for a pharmacist to review the case and recommend empiric antibiotics.

ANSWER

The patient's recent exposure to broad-spectrum antibiotics and recent residence at a facility puts this patient at increased risk of MDR bacteria. The selection of empiric antibiotics in a patient with septic shock necessitates the consideration of recent antibiotic exposure. Because the blood culture is currently growing *E. coli*, the risk of ESBL is high. Because *E. coli* is a known producer of Ambler class a β-lactamases, the empiric use of penicillins and cephalosporins would not be appropriate. Despite susceptibility to cephamycins, ESBL resistance can develop during therapy along with the acquisition of efflux pumps. Use of piperacillin/tazobactam would be effective in non-severe infections based on the efficacy of tazobactam in inhibiting ESBL; however, it may succumb to the inoculum effect in a severe infection such as this one. The use of carbapenems is the ideal empiric antibiotic in this patient. Ertapenem should be considered to spare anti-pseudomonal exposure. Considerations can also be given to administering a single dose of gentamicin to increase the likelihood of appropriate empiric antibiotics. The susceptibility to ertapenem would need to be verified by the microbiology laboratory. The continued use of vancomycin is appropriate based on the patient's recent surgery because of the risk of MRSA with an open surgery.

1. Kanj SS, Kanafani ZA. Current concepts in antimicrobial therapy against resistant gram-negative organisms: extended-spectrum beta-lactamase-producing Enterobacteriaceae, carbapenem-resistant Enterobacteriaceae, and multidrug-resistant *Pseudomonas aeruginosa*. Mayo Clin Proc 2011;86:250-9.

2. Martinez-Martinez L, Pascual A, Hernandez-Alles S, et al. Roles of betalactamases and porins in activities of carbapenems and cephalosporins against *Klebsiella pneumoniae*. Antimicrob Agents Chemother 1999;43:1669-73.

3. Peterson LR. Antibiotic policy and prescribing strategies for therapy of extended-spectrum beta-lactamase-producing Enterobacteriaceae: the role of piperacillin-tazobactam. Clin Microbiol Infect 2008;14:181-4.

4. Micek ST, Welch EC, Khan J, et al. Empiric combination antibiotic therapy is associated with improved outcome against sepsis due to gram-negative bacteria: a retrospective analysis. Antimicrobial Agents Chemother 2010;54:1742-8.

antibiotics decreases the rate of clinical failure, length of ICU stay, and may decrease mortality (Chant 2013). The ability of continuous or extended infusion to prevent the development of antibiotic resistance has been inconclusive.

NEW AGENTS

Tedizolid is a second-generation oxazolidinone that possesses enhanced in vitro efficacy compared with linezolid and maintains its activity again *Staphylococcus* spp. expressing the *cfr* gene, which results in resistance to linezolid. Tedizolid is approved for the treatment of acute bacterial skin and skin structure infections caused by susceptible isolates of gram-positive bacteria. Tedizolid also potentially displays lower rates of interactions with serotonergic agents, monoamine oxidase inhibitors, adrenergic agents, and foods with high tyramine content, as well as decreased rates of myelosuppression compared with linezolid (Lodise 2014; Flanagan 2013). Tedizolid may be considered in cases of linezolid-resistant strains or in patients on concomitant serotonergic agents or with pre-treatment myelosuppression.

Ceftazidime/avibactam was recently approved for the treatment of complicated intra-abdominal infections (when used in combination with metronidazole) and for complicated UTIs. Ceftazidime is an extended-spectrum cephalosporin with activity versus Enterobacteriaceae and *P. aeruginosa*. Avibactam is a non-β-lactam, β-lactamase inhibitor that is active versus Ambler class A (including *KPC*) and C β-lactamases and some Ambler class D β-lactamases (Coleman 2010). Unfortunately, avibactam is not active versus metallo-β-lactamase (class B)-expressing organisms. Because avibactam does have activity for *KPC*-producing strains, the use of ceftazidime/avibactam can considered over ceftolozane/tazobactam when *KPC* production is suspected.

Ceftolozane/tazobactam is a novel extended-spectrum cephalosporin with activity against Enterobacteriaceae and *P. aeruginosa*. Ceftolozane/tazobactam has activity against ESBL-producing (*CTX-M, OXA, TEM, SHV*) organisms and chromosomal *AmpC*-producing *P. aeruginosa*. It does not have activity versus *KPC* and metallo- β-lactamase (class B)-expressing organisms. Ceftolozane/tazobactam was recently approved for the treatment of complicated intra-abdominal infections (when used in combination with metronidazole) and for complicated UTI. The use of ceftolozane/tazobactam can be considered in cases in which *AmpC*-producing and some ESBL-producing strains are suspected.

CONCLUSION

Selection of empiric antibiotic therapy is an important factor to consider, especially with the higher rates of resistance within patients in the ICU. Empiric antibiotic therapy should be sufficiently broad-spectrum to cover the most likely pathogens while taking in account local susceptibility patterns.

Practice Points

Antibiotic resistance is a major problem encountered by clinicians within the ICU. Considerations should be made regarding the potential for resistant infections and the appropriate treatment:

- **Antibiotic resistance is associated with previous hospital stay, presence of chronic invasive devices, prior antibiotics, immunosuppression, and health care–associated pneumonia risk factors.**
- **Management of antibiotic resistance can include: development of institution treatment guidelines, selection of appropriate empirical antibiotic choices, selection of appropriate duration of antibiotic use, de-escalation of empirical antibiotic regimens, use of formulary restrictions, implementation of a multidisciplinary antibiotic management program, and use of pharmacokinetic and pharmacodynamic principles for antibiotic dose optimization.**
- **Treatment of MRSA and VRE often requires the use of agents other vancomycin, such as linezolid, daptomycin and ceftaroline (MRSA).**
- **Treatment of ESBL gram-negative infections often result in the use of carbapenems, although it can increase the risk of development of carbapenem-resistance.**
- **Treatment of resistant gram-negative infections may require the use of tigecycline, amikacin, and/or colistin.**
- **New agents can potentially aid in the treatment of resistant organisms.**

Antibiotics should be given in doses sufficient to take into account altered pharmacokinetic and pharmacodynamic properties of ICU patients in the presence of any renal or hepatic dysfunction. In patients who respond to initial therapy or when susceptibilities are known, de-escalation of therapy is recommended because it decreases the selection pressure for the development of resistance and potentially may decrease treatment cost. Optimal duration is important because prolonged duration of antibiotic therapy increases the emergence of resistance, drug cost and the potential for adverse drug events.

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Self-Assessment Questions

Questions 42-44 pertain to the following case.

A.K., a 74-year-old man, presents to the ED with a 2-day history of fever. He was recently hospitalized for 1 week with a dialysis graft infection caused by methicillin-resistant *Staphylococcus aureus* (MRSA) (MIC 1 mcg/mL); he was then treated with vancomycin for 3 weeks (completed 1 week ago) at the skilled nursing facility where he resides. A.K.'s medical history includes diabetes, hypertension, dyslipidemia, and end-stage renal disease requiring hemodialysis. His home drugs include glipizide, lisinopril, aspirin, and sevelamer. His physical examination is notable for temperature 38.6ºC, blood pressure 98/42 mm Hg, heart rate 98 beats/minute, respiratory rate 18 breaths/minute, and redness around the dialysis graft site. His laboratory values include WBC 19.4 x 10^3 cells/mm^3, hemoglobin 7.4 g/dL, hematocrit 22%, and platelet count 34,000 cells/mm^3. His peripheral blood cultures are currently growing gram-positive cocci in clusters. A.K. is admitted to the medical ICU for sepsis.

42. Which one of the following places A.K. at the greatest risk for the gram-positive cocci to be a multidrug resistant organism?

    A. Catheter site infection
    B. Sepsis
    C. Recent prolonged antibiotic therapy
    D. Hemodialysis

43. Which one of the following would be the most appropriate to start empirically for A.K.?

    A. Vancomycin
    B. Daptomycin
    C. Tigecycline
    D. Linezolid

44. Which one of the following mechanisms of resistance is most likely to have developed in A.K.?

    A. Chromosome mutation
    B. Enzymatic modification
    C. Efflux pump
    D. Altered target

45. A 52-year-old woman with diabetes presents with right flank pain. Her current laboratory test results include WBC 17.5 x 10^3 cells/mm^3, SCr 3.0 mg/dL, and her temperature in the ED was 37.1ºC. Her heart rate was 81 beats/minute and blood pressure 71/49 mm Hg. Urinalysis shows nitrite positive, leukocyte esterase positive, and WBC greater than 100 per high-power field. Her urine culture reveals the following:

Enterobacter cloacae

Antibiotic	Interpretation
Ampicillin	R
Ampicillin/sulbactam	R
Cefazolin	R
Ceftriaxone	S
Cefepime	S
Ciprofloxacin	R
Gentamicin	S
Levofloxacin	R
Nitrofurantoin	S
Piperacillin/tazobactam	R
Meropenem	S
Tetracycline	R

Which one of the following is best to recommend for this patient at this time?

A. Ceftriaxone
B. Cefepime
C. Gentamicin
D. Nitrofurantoin

Questions 46 and 47 pertain to the following case.

K.H. is a 53-year-old man with hypotension who is admitted into the ICU from a nursing home. He has a chronic Foley catheter and has a history of frequent UTIs treated with sulfamethoxazole/trimethoprim, levofloxacin, and most recently cefuroxime. His vital signs on admission include temperature 38.5ºC, heart rate 111 beats/minute, and blood pressure 85/52 mm Hg. Laboratory test results include WBC 17.1 x 10^3 cells/mm^3. Preliminary microbiological report reveals a urine culture growing 100,000 CFU/mL of *Klebsiella pneumoniae* with susceptibility pending.

46. Which of the following would is the best empiric antibiotic to start for K.H.?

    A. Ceftriaxone
    B. Ciprofloxacin
    C. Cefepime
    D. Ertapenem

47. K.H.'s blood culture came back positive for gram-negative bacilli, and the urine culture with the *Klebsiella pneumoniae* came back with the following initial susceptibility:

Klebsiella pneumoniae

Antibiotic	Interpretation
Ampicillin	R
Ampicillin/sulbactam	R
Cefazolin	R
Ceftriaxone	R
Cefepime	R
Ciprofloxacin	R
Gentamicin	R
Levofloxacin	R
Nitrofurantoin	R
Piperacillin/tazobactam	R
Meropenem	R
Tetracycline	R
Sulfamethoxazole/trimethoprim	R

A change to which one of the following antibiotics would be best to recommend for K.H.?

A. Ceftolozane/tazobactam
B. Tigecycline
C. Ceftazidime/avibactam
D. Amikacin

Questions 48 and 49 pertain to the following case.

T.S. is an 18-year-old man with no significant medical history. For the past week he has had upper respiratory tract symptoms; azithromycin, amoxicillin/clavulanate, and cefpodoxime were prescribed in attempted treatment. Today T.S. was admitted from the ED with shortness of breath requiring intubation. Tracheal aspirate reveals gram-positive cocci in clusters, and chest radiography reveals a dense consolidation in the left lower lobe.

48. Which one of the following is the mostly likely cause of T.S.'s infection?

    A. *Streptococcus pneumoniae*
    B. *Staphylococcus aureus*
    C. *Mycoplasma pneumoniae*
    D. *Moraxella catarrhalis*

49. Which one of the following is the best empiric antibiotic to recommend for T.S.?

    A. Ceftriaxone
    B. Oxacillin
    C. Linezolid
    D. Daptomycin

Questions 50–52 pertain to the following case.

A.S. is a 67-year-old man who has been in the surgical ICU for total colectomy. He required three colonic resections to fix a recurrent large bowel perforation. His antimicrobial therapy was changed at day 5 from cefoxitin to vancomycin, cefepime, and metronidazole as a result of poor response to initial therapy and microbiology reports. Subsequent intraoperative cultures revealed vancomycin-intermediate *Staphylococcus aureus* (VISA) and *E. coli*. A.S. was noted to have diffuse peritonitis visualized intra-operatively. His clinical status has remained critical; A.S. has not required the use of vasopressors but has an elevated WBC and intermittent fevers.

50. Which one of the following is the most likely mechanism of resistance for A.S.'s VISA?

    A. Altered peptidoglycan-binding protein 2
    B. Increased thickness of cell wall
    C. Efflux pump
    D. Alteration of peptidoglycan amino acid residue

51. Cultures from A.S.'s abdominal fluid came back with the following initial susceptibility for the *E. coli*:

    Escherichia coli

Antibiotic	Interpretation
Ampicillin	R
Ampicillin/sulbactam	R
Cefazolin	R
Ceftriaxone	R
Cefepime	R
Ciprofloxacin	R
Gentamicin	R
Levofloxacin	R
Nitrofurantoin	R
Piperacillin/tazobactam	I
Meropenem	S
Tetracycline	R
Sulfamethoxazole/trimethoprim	R

    Which one of the following is the most likely mechanism of resistance for A.S.'s *E. coli* infection?

    A. TEM-3
    B. *AmpC*
    C. NDM-1
    D. OXA-1

52. Which one of the following is best to recommend for A.S. to treat multiple organisms?

    A. Telavancin and piperacillin/tazobactam
    B. Linezolid and ertapenem
    C. Vancomycin and doripenem
    D. Daptomycin and colistin

53. A 54-year-old man with a history of cirrhosis and significant ascites is admitted for acute upper GI bleed and altered mental status. He was recently treated for UTI with first ceftriaxone then with levofloxacin, but had been in his usual state of poor health in the past 2 weeks until feeling worse

2 days ago. His ascitic fluid is sent for analysis and returns suggestive of spontaneous bacterial peritonitis. Which one of the following is best to recommend for this patient?

A. Ciprofloxacin
B. Ceftriaxone
C. Ampicillin/sulbactam
D. Ertapenem

Questions 54 and 55 pertain to the following case.

L.P. is a 62-year-old man who has a history of chronic decubitus ulcer. He was found to be hypotensive and is admitted to ICU for management. The area around the decubitus ulcer is foul smelling with frank pus emitting from the site and visible gray bone structure protruding. L.P. was taken to the operating room for washout of the area. The surgical bone culture reveals abundant gram-positive cocci in pairs and chains. Surveillance rectal culture grew vancomycin-resistant Enterococcus (VRE). L.P. has no known allergies.

54. Which one of the following is best to recommend as empiric treatment for L.P.'s infection?

    A. Ampicillin
    B. Vancomycin
    C. Ceftaroline
    D. Linezolid

55. One day later, L.P.'s wife brings in his home drug list which includes: aspirin, metoprolol, simvastatin, and fluoxetine. L.P.'s bone culture grew *Enterococcus faecalis* with the following susceptibilities:

Antibiotic	Interpretation
Ampicillin	S
Daptomycin	I
Gentamicin (Hi-Dose)	R
Linezolid	S
Streptomycin	R
Tetracycline	R
Sulfamethoxazole/trimethoprim	R
Vancomycin	R

    A change to which one of the following antibiotics would be best to recommend for L.P.?

    A. Ampicillin
    B. Tedizolid
    C. Ceftriaxone
    D. Telavancin

56. Two days ago, a 32-year-old woman with non–small-cell lung cancer received her first cycle of clinical trial chemotherapy. Since then she has received intravenous cefepime and vancomycin for fever. Blood cultures drawn from a port, placed a year ago, reveal MRSA. The patient continues to be febrile and hypotensive. Which one of the following places this patient at the greatest risk of multidrug resistant infection?

    A. Immunosuppressive therapy
    B. Treatment with vancomycin and cefepime
    C. Intravenous catheter
    D. Fever

Questions 57 and 58 pertain to the following case.

A.H., a 24-year-old man, was admitted to the neurosurgery ICU with continued fever and hypotension. He has a history of motor vehicle crash that resulted in an intracranial bleed requiring a craniotomy and the placement of a ventricular peritoneal shunt to remove excess CSF. The shunt was previously complicated by infection with *Pseudomonas aeruginosa*, resulting in treatment with 3 weeks of cefepime. After some initial improvement, A.H.'s mental status has declined, and he is now febrile and hypotensive.

57. Which one of the following is the best empiric gram-negative antibiotic to start for A.H.?

    A. Cefepime
    B. Piperacillin/tazobactam
    C. Meropenem
    D. Ciprofloxacin

58. It is one month later and A.H. has completed a regimen of antibiotics for the shunt infection. He is now experiencing shortness of breath because of suspected pneumonia. A.H.'s tracheal culture grew *Pseudomonas aeruginosa* with the following initial susceptibility:

    Pseudomonas aeruginosa

Antibiotic	Interpretation
Cefepime	R
Ciprofloxacin	R
Gentamicin	R
Levofloxacin	R
Piperacillin/tazobactam	R
Meropenem	R

    Which one of the following would be the best antibiotic to start for A.H.?

    A. Imipenem/cilastatin 2 g continuous infusion
    B. Ceftazidime/avibactam 2.5 g every 8 hours
    C. Colistin 5 mg/kg/day divided every 8 hours
    D. Tigecycline 200 mg then 100 mg twice daily

Questions 59–61 pertain to the following case.

L.A. is a 68-year-old woman with end-stage kidney disease secondary to poorly controlled diabetes mellitus. She is receiving hemodialysis three times weekly. Her medical history also includes hypertension and morbid obesity. L.A.'s current home drugs include insulin glargine, insulin aspart,

lisinopril, and metoprolol. She complains of shortness of breath, fever, chills, and loss of appetite over the past 2 days. Examination results are: temperature 38.6ºC , respiratory rate 31 breaths/minute, heart rate 120 beats/minute, and blood pressure 86/52 mm Hg. Chest radiography reveals a dense consolidation in the right lower lobe. L.A. is started on norepinephrine and admitted to the ICU.

59. Which one of the following is best to start as empiric therapy for L.A.?

    A. Linezolid and moxifloxacin
    B. Ceftriaxone and azithromycin
    C. Vancomycin and meropenem
    D. Cefepime and gentamicin

60. The team decides to start L.A. on linezolid, doripenem, and gentamicin. Which one of the following would best justify the empiric aminoglycoside for L.A.?

    A. Provide synergy with doripenem
    B. Decrease mortality
    C. Increase likelihood of appropriate antibiotic
    D. Decrease development of resistance

61. L.A.'s cultures from the tracheal aspirate initially grew *Pseudomonas aeruginosa*. Her antibiotics were appropriately de-escalated based on culture results; she responded well and was extubated. After 2 weeks in the ICU, L.A.'s condition worsened and she required re-intubation. The patient had a bronchoalveolar lavage that grew VISA. Which one of the following would be the best strategy to prevent the spread of L.A.'s VISA to other patients?

    A. Use of selective digestive tract decontamination
    B. Use of chlorhexidine body wash
    C. Hand hygiene
    D. Antibiotic stewardship

Learner Chapter Evaluation: Antimicrobial Resistance in the ICU.

As you take the posttest for this chapter, also evaluate the material's quality and usefulness, as well as the achievement of learning objectives. Rate each item using this 5-point scale:

- Strongly agree
- Agree
- Neutral
- Disagree
- Strongly disagree

37. The content of the chapter met my educational needs.
38. The content of the chapter satisfied my expectations.
39. The author presented the chapter content effectively.
40. The content of the chapter was relevant to my practice and presented at the appropriate depth and scope.
41. The content of the chapter was objective and balanced.
42. The content of the chapter is free of bias, promotion, or advertisement of commercial products.
43. The content of the chapter was useful to me.
44. The teaching and learning methods used in the chapter were effective.
45. The active learning methods used in the chapter were effective.
46. The learning assessment activities used in the chapter were effective.
47. The chapter was effective overall.

Use the 5-point scale to indicate whether this chapter prepared you to accomplish the following learning objectives:

48. Analyze strategies for minimizing the development and spread of antibiotic resistance.
49. Evaluate the differences in mechanism of antibiotic resistance.
50. Develop a treatment plan for infections caused by resistant gram-positive organisms.
51. Compose an antimicrobial regimen for resistant gram-negative infections.
52. Please provide any specific comments related to any perceptions of bias, promotion, or advertisement of commercial products.
53. Please expand on any of your above responses, and/or provide any additional comments regarding this chapter:

Questions 54–56 apply to the entire learning module.

54. How long did it take you to read the instructional materials in this module?
55. How long did it take you to read and answer the assessment questions in this module?
56. Please provide any additional comments you may have regarding this module: